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Original Communications

THE AUTONOMIC MECHANISM OF HEAT CONSERVATION AND DISSIPATION

I. EFFECTS OF HEATING THE BODY

EVIDENCE FOR THE EXISTENCE OF CAPILLARY DILATOR NERVES IN ANTERIOR ROOTS

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AMONG the important functions of the skin are the conservation and dissipation of heat for the purpose of maintaining a constant central temperature. The thoracolumbar or sympathetic* division of the autonomic nervous system plays a major role in subserving this function. Much can be learned concerning this function of the sympathetic system by studying the skin reactions of patients who have had various operative procedures performed on the nervous system (particularly sympathetic). We have studied the effects of heat, cold, adrenaline, and pilocarpine on a series of such patients. We have studied the effect of heat on a larger series than that reported here, but this group is representative.

Our studies have involved observations concerning three factors in heat regulation by the skin: sudomotor, vasomotor, and pilomotor. There is evidence that responses may occur in each of these systems and be governed by (1) the end organ itself (sweat gland, arteriole and capillary, and pilomotor muscle), (2) by a reflex through the spinal cord, and (3) by central (hypothalamic) control. For convenience we will hereinafter refer to these three mechanisms as first, second, and third order reactions, respectively.

Sweat Gland.—We have presented evidence[1] that the sweat gland itself may respond to a heat stimulus after its nerve fiber has degenerated, if the skin is covered.

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*Sympathetic is used in contradistinction to the parasympathetic (craniosacral) division.

Reflex sweating (second order reaction) after complete transverse lesions of the cord[2] and thermoregulatory sweating (third order reaction)[3] are well-known phenomena.

Vasomotor System of Skin.—One must give separate consideration to capillaries and arterioles. The first order mechanism is easily demonstrated in patients after postganglionic degeneration by placing them in hot or cold environments or by placing hot or cold objects on the sympathectomized part.

We have not been successful in demonstrating the second order vasomotor reaction convincingly, but it probably functions to some degree. We feel that the tests should be carried out on spinal patients or spinal animals.[4] On one spinal patient we were able to elicit no significant contralateral changes in the skin temperature of the toes when the opposite extremity was immersed in cold water at a time when the cord reflexes were intact. Gibbon and Landis[5] found that, when the forearms of normal persons in a cool room were immersed in warm water, the temperature of the toes would rise considerably. This, however, is most likely a third order mechanism, and not reflex to any great extent through the cord. They also gave evidence to verify this reasoning.

That there is a third order (hypothalamic) vasomotor control of arterioles is well known.[6] We are adding to this strong evidence that capillary dilatation is centrally controlled.

Pilomotor System.—We have always been able to elicit a local pilomotor response to pinching in sympathectomized skin areas. Pilomotor activity en masse in spinal man and third order or centrally controlled pilomotor activity are known to exist.[6] Our studies would indicate that the first and third order mechanisms are by far the most important and that the reflex mechanism through the cord normally plays a very minor role.

No true parasympathetic (craniosacral) fibers innervating the sweat glands, arterioles, or pilomotor muscles of the skin have been demonstrated. These structures are controlled by the thoracolumbar or sympathetic division only. However, many investigators have demonstrated that there are two types of fibers in the sympathetic system, and it is now generally accepted that two types do exist, namely, cholinergic and adrenergic.[7-12] It does not seem possible that one type of fiber could subserve all the functions which are known to take place in the skin structures, nor can it be assumed that the dual function ascribed to the peripheral activity of hormones can exist without postulating a dual innervation. For example, there is evidence for the existence of vasodilator as well as vasoconstrictor fibers to the arterioles of the skin. Our study does not prove or disprove that there are vasodilator fibers to arterioles, but Lewis and Pickering,[13] by ingenious experiments, have produced evidence that they exist. Also, there is some evidence that, when cholinergic fibers are active, the adrenergic ones are inhibited, and vice versa. For example, in postoperative hyperthermia, which,

we believe, is a manifestation of extreme overactivity of the heat-conserving mechanism, we have observed marked vasoconstriction, waves of pilomotor activity, and absence of sweating. In such a case it has been very difficult, if not impossible, to break through the sweat "inhibition" with pilocarpine. Lastly, it might be assumed that adrenaline would inhibit sweating. Although we have not tested this, Higier[7] regards it as proved.

The efficiency with which the skin may conserve or dissipate heat in man is quite remarkable. In hyperthermia the skin may be icy cold when the circulating blood has a temperature of 108° F.

We should like to emphasize that in this, as in other studies involving neurophysiology, normal reactions are functionally integrated toward a purposeful end. The third order, or centrally controlled mechanism, is dominant. The general location of primary heat-conserving and heat-dissipating centers in the hypothalamus[6] is known,[14] and this head ganglion responds to the needs of the organism. So far as the thermoregulatory control is concerned, the response is standard. In heat conservation there are vasoconstriction, pilomotor activity, and absence of sweating. In heat dissipation there is vasodilatation of the arterioles of the skin, followed, when the need is extreme, by capillary dilatation, sweating, and absence of pilomotor activity. The higher centers, i.e., the frontal lobes, impel the hypothalamus under certain conditions to produce skin reactions which do not follow the usual pattern of thermoregulatory activity. The combination of vasoconstriction and sweating which occurs with fear and emotional blushing are examples of such a reaction.

It does not follow that, because a certain stimulus causes vasoconstriction in the skin, it will also cause vasoconstriction in the deeper vessels. The reverse may be true, but in any case the responses will depend upon the biologic objective. Talbot[15] has made some very extensive studies of skin temperature under varying conditions. He found that during exercise there is a fall in skin temperature, even though there is a rise in body temperature. In this case heat elimination does not keep pace with heat production. During the half hour after activity has ceased, the skin temperature rises frequently to a point much higher than that which preceded exercise. Benedict and Parmenter[16] also found a lowering of skin temperature during exercise. These results can be explained partly by vasoconstriction in the skin to mobilize blood where it is most needed.

Again, the responses obtained when an anterior spinal root is artificially stimulated are vasoconstriction, pilomotor reaction, and sweating,[17] i.e., a heterogeneous, purposeless combination which should not be accepted as indicating integration of function.

Of the three thermoregulatory responses in man, sweating and vasomotor control are the most important; the pilomotor reaction is only a

vestige of an important function in animals and birds. Sweat can serve its purpose of having a cooling effect only in proportion to evaporation. If the latter cannot occur, sweating must surely be of little value in dissipating heat. Vasodilatation is undoubtedly the most important factor in heat dissipation in man.

Although skin temperature may be accepted as a reasonably accurate index of the rate of heat dissipation, this is true only within certain limits. Heat may be dissipated in two ways by vasodilatation. The arterioles may open, thereby increasing the minute volume flow of blood subject to radiation. In this case, and from a purely physical standpoint, skin temperature would approach the central temperature as a limit. Actually, in our experience, it has never reached the central temperature. If the arterioles are in a state of maximal dilatation, numerous capillaries may open, which would increase the amount of blood exposed to radiation, and reduce its velocity. Under these conditions the skin temperature will no longer be an index to the rate of heat dissipation. Indeed, it is conceivable that the skin may become colder even when the rate of heat dissipation has increased. When the capillary bed opens up, the skin presents a sunburn flush, but its temperature does not always exceed that of an unflushed zone. Although capillary and arteriolar dilatation probably occur to some degree concomitantly, we have seldom seen visible evidence of flushing unless the need for heat dissipation was great.

The criticism might be offered that the skin may act as an inanimate body under the conditions of these experiments. We feel, however, that the presence of circulating blood in the skin clearly dispels this criticism. In fact, the temperature of the skin is at all times a function of the temperature of the blood and of the factors which control its rate of flow. To obtain data relevant to this problem was the exact purpose of these experiments. The cabinet was always twenty or more degrees warmer than the body of the patient, and yet the skin temperature never at any time rose as high as the body temperature because the skin does not respond as an inanimate body.

It might also be supposed that sweating would interfere with the results. Some of the experiments were done with the subject under the influence of atropine, and others without atropine. When atropine was used, in some cases the skin remained thoroughly dry throughout the experiment, but, in any case, the results were always the same with or without sweating—that is, in patients who had had a unilateral sympathectomy the temperature of the fingers or toes was the same on both sides at the end of the experiment. We feel that this fact in itself bears out our contention that sweat has little or no influence on the temperature of the skin except through the cooling effect of evaporation. Under the conditions of these experiments the chance for evaporation was absent or minimal.

METHOD

Skin temperatures were taken with a Tycos Dermatherm.* Basal readings were made shortly before placing the patient in the cabinet. The patient was exposed for twenty to thirty minutes at a constant room temperature before the basal readings were taken. He was then placed on his back in a Burdick fever therapy cabinet† which had attained a maximum temperature with dry heat. The patient's head remained outside the cabinet. At the termination of the experiment, which lasted forty-five minutes to an hour, the cabinet was opened and the skin temperatures taken. The mouth temperature, pulse rate, and blood pressure were followed. The thermometer of the dermatherm was checked for each set of readings, and the absolute temperature of the skin was calculated in degrees centigrade.

We studied the effect of external heat, the inductotherm, and the inductotherm after a hypodermic injection of atropine (gr. 1/75) to prevent sweating and to encourage the most marked vasomotor reactions. The inductotherm plus atropine produced the most marked and interesting responses.

EFFECTS OF HEATING THE BODY

Expermiment 1.—Nov. 24, 1939. Effect of dry heat. Ralph McG., aged 55 years, one hundred twenty days after the removal of the left inferior cervical and the upper six dorsal ganglia (Table I).

TABLE I

EFFECT OF HIGH TEMPERATURE ON SKIN

PART	SKIN TEMPERATURE (°C)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	31.6	31.6		31.7	32.7	+0.1	+1.1
Cheek	31.1	31.1		34.7	32.7	+3.6	+1.6
Neck	32.1	32.6		32.2	33.2	+0.1	+0.6
Chest	32.1	32.1		32.2	34.2	+1.1	+2.1
Arm	31.6	31.6		32.7	33.7	+1.1	+2.1
Forearm	31.6	32.1		32.7	33.7	+1.1	+1.6
Finger	31.6	32.1		32.7	32.7	+1.1	+0.6
Abdomen	33.1	33.1		32.7	32.7	−0.4	−0.4
Thigh	32.1	32.1		32.2	32.2	+0.1	+0.1
Calf	32.1	32.1		32.2	32.2	+0.1	+0.1
Ankle	31.6	31.1		32.2	32.2	+0.6	+1.1
Mouth temperature	36.77° C. 98.2° F.			36.88° C. 98.4° F.			
B. P.	114/70			96/64			
Pulse	96			104			
Time (P.M.)	2:26		2:30	3:20			
Remarks	Basal		In cabinet	Cabinet opened			

Observations: There was good sweating over the body except in the sympathectomized zone. No flushing of the skin was seen.

*Differences between first and last readings.

Room temperature, 26.7° C.; temperature of cabinet, 45.0° C. (dry heat).

Comment.—The left middle finger was only 0.5° C. warmer than the right at the beginning.‡ The temperatures of the two were equal at the end of the experiment; they had become only slightly warmer. The mouth temperature rose only 0.2° F.

Experiment 2.—Dec. 4, 1939. Effect of dry heat and atropine. Ralph McG., 130 days after operation. (Table II.)

*Taylor Instrument Company, Rochester, N. Y.

†We wish to thank the members of the Department of Medicine for allowing us to use the Burdick cabinets, and Miss Genevieve Wendlandt for her helpful cooperation in carrying out the experiments.

‡The difference in the temperatures of the fingers on the two sides was no greater than this after the operation.

Comment.—The temperatures of the middle fingers were equal at the beginning and end of the experiment; they rose 3.7° C. On the whole, the temperatures rose higher than in the previous experiment, and the mouth temperature rose 1° F. The demarcation of flushing on the face, as noted below Table II, was marked.

TABLE II

EFFECT OF HIGH TEMPERATURE AND ATROPINE ON SKIN

PART	SKIN TEMPERATURE (°C)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	32.5	32.5		32.7	32.7	+0.2	+0.2
Cheek	32.5	32.5		33.2	31.7	+0.7	−0.8
Neck	31.5	31.5		32.7	32.2	+1.2	+0.7
Chest	33.0	33.0		34.2	35.2	+1.2	+2.2
Arm	33.0	33.0		34.2	34.7	+1.2	+1.7
Forearm	32.5	32.5		33.7	34.2	+1.2	+1.7
Finger	31.5	31.5		35.2	35.2	+3.7	+3.7
Abdomen	33.0	33.0		34.2	34.2	+1.2	+1.2
Thigh	32.0	32.5		34.2	34.2	+2.2	+1.7
Calf	32.0	32.0		34.2	34.7	+2.2	+2.7
Ankle	32.0	31.5		34.7	34.7	+2.7	+3.2
Mouth temperature	36.66° C. 98.0° F.			37.22° C. 99.0° F.			
B. P.	90/64			92/66			
Pulse	96			120			
Time (P.M.)	3:15		3:18	4:15			
Remarks	Basal Atropine (gr. $\frac{1}{75}$) H		In cabinet	Cabinet opened			

Observations.—There were complete absence of sweating, marked flushing on the normal side of the face and on the normal ear and no flushing on the face and ear of the denervated side. The line of demarcation was sharp and definite.

*Differences between first and last readings.

Room temperature, 27.7° C.; temperature of cabinet, 45.0° C. (dry heat).

TABLE III

EFFECT OF INDUCTOTHERM ON SKIN

PART	SKIN TEMPERATURE (°C)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	31.5	31.5		33.4	32.9	+1.9	+1.4
Cheek	31.5	31.5		33.4	32.9	+1.9	+1.4
Neck	30.5	31.5		33.4	33.4	+2.9	+1.9
Chest	32.0	31.5		32.4	33.4	+0.4	+1.9
Arm	32.0	32.0		31.9	33.9	−0.1	+1.9
Forearm	32.0	32.0		33.4	33.9	+1.4	+1.9
Finger	31.0	31.0		32.9	32.9	+1.9	+1.9
Abdomen	32.0	32.0		32.4	31.9	+0.4	−0.1
Thigh	31.0	31.5		32.4	32.4	+1.4	+0.9
Calf	31.5	31.5		32.4	31.9	+0.9	+0.4
Ankle	30.5	30.0		32.4	31.9	+1.9	+1.9
Mouth temperature	36.66° C. 98.0° F.			38.0° C. 100.4° F.			
Pulse	92			120			
Time (A.M.)	9:24		9:30	10:45			
Remarks	Basal		In cabinet Inducto-therm	Cabinet opened			

Observations.—Sweating was profuse over the body except in the sympathectomized zone. At the end of experiment there was marked demarcation of flushing on the face. Flushing was absent on the left (sympathectomized) side of face and ear, and was marked on the right ear and right side of the face.

*Differences between first and last readings.

Room temperature, 26.7° C.; temperature of cabinet, 48.33° C.

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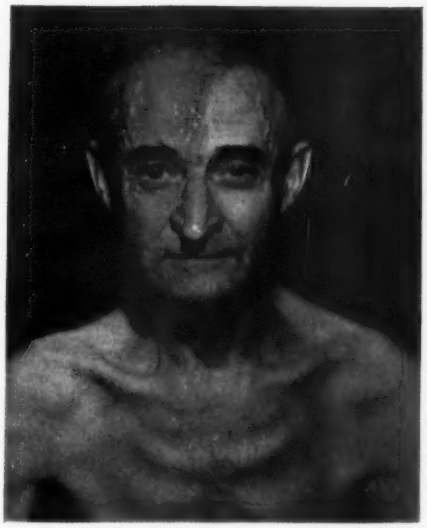

Fig. 1.—Ralph McG., Experiment 3, demonstrating sweating and flushing on the right side of the face only; the left (sympathectomized) side is dry and pale.

This result, as far as flushing is concerned, was always obtained after unilateral cervicodorsal ganglionectomy when the body was heated sufficiently to raise the central temperature, and even though sufficient atropine was administered to prevent sweating.

Experiment 3.—Dec. 5, 1939. Effect of inductotherm.* Ralph McG., 131 days after operation. (Table III.)

Comment.—The temperatures of the middle fingers were equal at the beginning and end of the experiment, and, on the whole, the temperatures did not rise as high as in Experiment 2, although the mouth temperature rose 2.4° F. The demarcation of flushing on the face is given below Table III. (See Fig. 1.)

Experiment 4.—Effect of atropine at room temperature. Ralph McG., 131 days after operation.

Comment.—This was a control experiment, carried out at room temperature (78.0° F.). Atropine (gr. $\frac{1}{75}$) was injected hypodermically, and observations were recorded as in Tables I to III. For a period of an hour there was no rise in skin temperature and no flushing of the face. The mouth temperature fell 0.3° F., and the average fall in skin temperature was 1° C. The blood pressure remained constant, although the pulse rate rose from 96 to 116 beats per minute.

Experiment 5.—Dec. 16, 1939. Effect of inductotherm. Margaret B., aged 31 years, one year after removal of the left inferior cervical and upper three dorsal ganglia (Table IV).

Comment.—The left middle finger was 2.5° C. warmer than the right at the beginning of the experiment. The temperatures were equal at the end of the experiment; that of the right had risen 2.9° C. The mouth temperature rose 2.6° F. There was capillary flushing of only the right side of the face, as noted below Table IV.

TABLE IV

EFFECT OF INDUCTOTHERM ON SKIN

PART	SKIN TEMPERATURE (°C)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Finger (middle)	30.1	32.6		33.0	33.0	+2.9	+0.4
Mouth temperature	37.2+ C. 99.0° F.			38.7° C. 101.6° F.			
Pulse	84			120			
B. P.	106/70			110/70			
Time (P.M.)	2:15		2:30	4:15			
Remarks	Basal		In cabinet Inducto-therm	Cabinet opened			

Observations.—The head, face, and teeth ached and throbbed at 3:30 P.M. only on the right side (operation had been done for atypical neuralgia on left). There was capillary flushing on the right side of the face; the left remained pale. The demarcation at the midline was definite.

*Differences between first and last readings.

Room temperature, 26.7° C.; temperature of cabinet, 46.7° C.

Experiment 6.—Feb. 3, 1940. Effect of inductotherm and atropine. Mabel R., aged 23 years, 380 days after section of sensory roots C 8 to T 4, inclusive, on both sides, and 331 days after removal of the right inferior cervical and upper two dorsal ganglia (Table V).

Comment.—The right middle finger was 6° warmer than the left at the beginning, and 1° warmer at the end, of the experiment; the temperature of the left rose 8°. The differences in the thumbs and palms were of the same magnitude. The mouth temperature rose 1.8° F. The flushing response is described under Table V.

The oxygen and carbon dioxide content of blood from the median basilic vein was determined with the patient resting at room temperature. (See Table VI.)

*In the Burdick fever therapy cabinet, the inductotherm mechanism is so arranged that it affects the entire body.

TABLE V

EFFECT OF INDUCTOTHERM PLUS ATROPINE ON SKIN

PART	SKIN TEMPERATURE (°C.)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	32.9	33.4		32.4	33.9	−0.5	+0.5
Cheek	32.9	32.9		33.4	34.4	+0.5	+1.5
Nose	31.9	31.9		32.9	33.4	+1.0	+1.5
Ears	32.9	32.4		32.4	32.9	−0.5	+0.5
Thumb	33.4	27.4		36.4	35.9	+2.0	+8.5
Finger (middle)	33.4	27.4		36.4	35.4	+2.0	+8.0
Mouth temperature	37.0° C. 98.6° F.			38.0° C. 100.4° F.			
Pulse	88			148			
B. P.	114/70			110/62			
Time (P.M.)	2:00		2:05	3:05			
Remarks	Basal Atropine (1/75 gr.)H		In cabinet	Cabinet opened			

Observations.—The skin remained dry throughout the test. At the end of the experiment there was a distinct pink flush of the left side of the face, arm, and hand. The right side of the face, arm, and hand were pale. There was a definite line of demarcation on the face.

*Differences between first and last readings.

Room temperature, 27.2° C.; temperature of cabinet, 46.7° C.

TABLE VI

HAND	OXYGEN (VOL. %)	CARBON DIOXIDE (VOL. %)
Right	10.30	49.7
Left	8.15	50.9

These results would indicate a greater minute volume flow of blood in the warmer (denervated) right hand.

TABLE VII

EFFECT OF INDUCTOTHERM PLUS ATROPINE ON SKIN

PART	SKIN TEMPERATURE (°C.)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	31.9	32.4		33.6	34.1	+1.7	+1.7
Cheek	31.9	31.9		34.1	34.6	+2.2	+2.7
Nose	30.9	29.9		32.1	32.6	+1.2	+2.7
Ears	30.4	30.4		33.1	33.1	+2.7	+2.7
Thumb	29.4	28.9		35.6	35.6	+6.2	+6.7
Finger (middle)	28.4	27.9		35.6	35.6	+7.2	+7.7
Ankle	31.9	31.4		35.6	36.1	+3.7	+4.7
Toe	32.9	29.4		37.1+	37.1+	+4.2+	+7.7+†
Mouth temperature	37.2° C. 99.0° F.			39.1° C. 102.4° F.			
Pulse	66			136			
B. P.	204/140			170/130			
Time (P.M.)	3:15		3:20	4:30			
Remarks	Basal Atropine (gr. 1/75)H		In cabinet	Cabinet opened			

Observations.—There was no flushing on the face. The left thigh, calf, and foot had a definite pink flush, compared to the pale right thigh, calf, and foot. Sweating occurred only on that part of the back in contact with linen.

*Differences between first and last readings.

†Figures off the instrument scale.

Room temperature, 27.2° C.; temperature of cabinet, 48.3° C.

Experiment 7.—Feb. 5, 1940. Effect of inductotherm and atropine. Eline R., aged 39 years, 449 days after section of anterior and posterior roots T 1 to T 5, inclusive, on both sides, and 504 days after section of the splanchnic nerves and removal of the first and second lumbar ganglia on the right (Table VII).

Comment.—The right large toe was 3.5° warmer than the left at the beginning of the experiment. The temperatures of both rose to 1° off the scale of the instrument but were roughly equal at the end. The mouth temperature rose 3.4° F. There was no flushing on the face, but the left thigh, calf, and foot showed a definite pink flush; the corresponding parts on the right remained pale.

Experiment 8.—Feb. 4, 1940. Effect of inductotherm and atropine. Leah C., aged 33 years, 347 days after section of the anterior and posterior roots T 1 to T 5, inclusive, on both sides, and bilateral chordotomy, and sixteen days after removal of the stellate and first dorsal ganglia on the right (Table VIII).

TABLE VIII

EFFECT OF INDUCTOTHERM PLUS ATROPINE ON SKIN

PART	SKIN TEMPERATURE (°C.)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	34.6	35.1		35.2	34.7	+0.6	−0.4
Cheek	34.6	34.6		35.2	35.2	+0.6	+0.6
Nose	34.6	34.6		35.2	34.7	+0.6	+0.1
Ears	36.1	36.1		35.7	35.7	−0.4	−0.4
Finger (middle)	34.6	32.6		37.7	37.2	+3.1	+4.6
Mouth temperature	37.2° C. 99.0° F.			38.6° C. 101.4° F.			
Pulse	66			144			
B. P.	178/120			130/90			
Time (P.M.)	3:05		3:25-3:30	4:30			
Remarks	Basal		Atropine (gr. 1/75): In cabinet	Cabinet opened			

Observations.—There was a small amount of moisture on the palm of the left hand only. Otherwise, the skin was dry. The entire face remained pale, without flushing. There was not the slightest evidence of any difference on the two sides. There was a definite difference, however, in the hands and arms on the two sides. The left hand and arm were flushed, whereas the right remained pale.

*Difference between first and last readings.

Room temperature, 26.0° C.; temperature of cabinet, 48.3° C.

Comment.—The chordotomy was bilateral at the level of T 3; a cataract knife was inserted straight into the cord just anterior to the dentate ligament. The sections were 3 mm. deep and 2.5 mm. wide. We do not feel that the chordotomy influenced sweating. In five such cases in which chordotomy was done we were unable to detect any change in thermoregulatory sweating or anything unusual about the skin temperatures after the heat test, unless, in this case, the difference in the temperature of the toes and ankles was caused by the chordotomy.

The right middle finger was 2° warmer than the left at the beginning, and 0.5° warmer at the end of the experiment; the temperature of the left rose 4.6°. The mouth temperature rose 2.4° F. The interesting flushing response is described in Table VIII.

DISCUSSION

As was reported in a recent paper,[1] we have found that section of the anterior roots T 1 to T 5, inclusive, on both sides, practically abolishes

thermoregulatory sweating on the face. It may be diminished down to the level of T 2 or T 3, but sweating is usually abundant on the neck and normal on the upper extremities. After removal of the inferior cervical and upper two dorsal ganglia, sweating is abolished on the ipsilateral side of the face, neck, and upper extremity, and the line of demarcation is sharp. We believe that the distribution of fibers to arterioles and capillaries closely agrees with the distribution to sweat glands.

Substantial changes in skin temperature after ganglionectomy occur only on the hands, fingers, ankles, and toes and are most marked on the tips of the fingers and toes. Although it is sometimes stated that the ipsilateral side of the face is warmer in Horner's syndrome, we have never been able to verify this and find that the ears, nose, and cheeks do not become relatively warmer after cervicodorsal ganglionectomy before or after time for postganglionic degeneration has elapsed, even though the relative warmth of the hand and fingers may be marked.

The relative increase in the temperature of the hand and fingers after cervicodorsal ganglionectomy may vary from no change to a difference of 5° or 6° C., and this is true either before or after degeneration has occurred. If the hand is warmer after ganglionectomy, it remains warmer than its mate (in the nonvasospastic subject). At least this has been true in our cases for as long as 1.5 years after operation. We have not encountered a single case in which the sympathectomized hand became colder in the absence of vasospastic disease. There was no significant relative change after operation in Ralph McG. (Experiment 1). We have found that this is usually true in patients of his age (55 years), or older. After lumbar ganglionectomy, however, there has always been a relative rise in temperature of the toes, in our experience. The change in temperature of the skin after sympathectomy is an indication not only of the flexibility of the arterioles, but of the degree of vasospasm imposed through the sympathetics. It appears that this control is diminished with age, and this may be more true of the upper than of the lower extremities.

In the cases reported here, the maximum relative difference in the temperature of the fingers after unilateral cervicodorsal ganglionectomy was 6° C. (Mabel R., Experiment 6). The difference in the toes of Eline R. (Experiment 7) after lumbar ganglionectomy was 7° C.

The skin temperature never became equal to the mouth temperature with any method of heating. Excepting the hands and feet, the skin temperature rises about as much as the mouth temperature.

No matter what the difference was in the temperature of the fingers or toes on the two sides at the beginning, the two sides were equal at the end of a heating experiment. Lewis and Pickering[13] stated that denervated skin rarely becomes as warm as the normal side when heated,

and they attribute the failure of maximal dilatation to interruption of vasodilator fibers. Our results do not agree with this, and for a definite reason. Their subjects were placed in a heating cabinet with the hands outside. Hence they were measuring only the central thermoregulatory effect on the hands. The sympathectomized hand would not be expected to warm under these conditions, at any rate not more than the rise in blood temperature. The hands of our subjects were in the heating cabinet, and hence we were measuring the first order, or peripheral action, of heat on the vessel itself. Kunkel, Stead, and Weiss[18] found that local heat of 43° C. produces nearly complete vasodilatation in the skin.

There are three different methods of studying a sympathectomized hand and its reaction to a change in temperature: (1) The body may be subjected to a change in temperature in a cabinet with the hands outside;[13] (2) the body may be placed in a constant temperature cabinet with the hands outside and the outside temperature changed (Ascroft[19]); and (3) the entire body may be placed in a cabinet the temperature of which is changed (Hyndman and Wolkin,[20] experiments herein reported). In the first method one studies the third order reaction alone. Lewis and Pickering[13] found that, under these circumstances, when the environmental temperature of the body was changed, the skin temperature of the normal hand changed accordingly, that is, it increased when the body was heated. The sympathectomized hand, however, underwent no change because its central sympathetic connections had been interrupted.

In the second method one studies, in our opinion, essentially the first and second order reactions.

In the third method one studies a combination of first, second, and third order reactions. We found, as demonstrated in this report, that, when the entire body is heated with the hands inside the cabinet, the skin temperatures of the sympathectomized and normal fingers finally always become equal, no matter what the difference may be at room temperature. In an investigation of the effect of severe cold, the results of which are to be published,[20] we found that, when the nude subject was placed in a refrigerator at a temperature of 0° to 6° C., the temperature of the fingers on both sides declined markedly, but not quite as much on the sympathectomized as on the normal side.

The fact that the temperatures of the fingers on the two sides were always equal at the end of our heating tests would indicate that arteriolar vasodilatation becomes maximal. After sympathectomy has produced some dilatation of arterioles, the latter can be dilated still further by applying heat.

If we let A represent the vasodilation, or, rather, the increase in skin temperature that results from only the local effect of heat on the vessel itself (first order reaction), then the fact may be expressed as follows:

The relative increase in the temperature of a finger after sympathectomy plus A equals the increase in the temperature of the normal finger that results from centrally controlled (second and third order) vasodilation,* plus A. This is true if the parts measured are subjected to the same external heat, and if this heat is sufficient to bring about maximal vasodilation.

EVIDENCE FOR THE EXISTENCE OF CENTRALLY CONTROLLED CAPILLARY DILATOR FIBERS

We refer to *capillary* dilator fibers because our conclusions depend upon a visible change due to capillary dilatation. Capillary dilatation may be only a part of a general vasomotor dilator mechanism. The evidence for the existence of an active vasodilator mechanism in general is summarized by Starling.[21] Stimulation of the cut end of the chorda tympani causes dilatation of the vessels in the submaxillary gland. Other dilator nerves are the small petrosal nerve to the parotid gland, the lingual nerve to the blood vessels of the tongue, and the pelvic visceral nerves to those of the penis. There are two anatomic differences between these examples and the skin dilators which we have observed. The cell bodies of the fibers in the former lie close to the structures which they innervate, as is generally the case with parasympathetics, whereas no comparable cell bodies have been demonstrated in the skin. Secondly, fibers in the former case leave in company with craniosacral nerves, whereas those to the skin vessels are strictly thoracolumbar. In the dog, dilatation of the vessels of the soft palate and gums can be produced by stimulation of the cervical sympathetic of the same side, and these fibers may be homologous with those of the skin. Starling points out that vasodilator nerves can be demonstrated in mixed peripheral nerves, i.e., sciatic, by stimulating the peripheral cut end with repeated induction shocks at slow intervals, or by taking advantage of the apparent fact that the degeneration times of vasoconstrictors and vasodilators are unequal.

Stimulation of the peripheral end of a sensory root causes dilatation of skin vessels in the distribution of the sensory nerve.[22] It is probably because of this fact that there has been a tendency to believe that the sympathetic vasodilators of the skin course with the posterior roots. We believe that this antidromic response, as demonstrated by Bayliss, operates in the same manner as does the axon reflex after the intra-

*We do not wish to commit ourselves on what proportion of this central arteriolar vasodilation is active and what proportion is accounted for by inhibition of vasoconstriction. The conclusion which we should be forced to draw at present is that, since the temperatures are always equal on the two sides at the end of a heating experiment, there is no evidence of the existence of arteriolar vasodilator nerves. We cannot quite correlate this conclusion with the results of Lewis and Pickering.[13] If the patient's hands are outside the heating cabinet, and hence constantly at room temperature, we might say that the sympathectomized hand exhibits a first order vasoconstriction incident to room temperature and that this first order response in the normal hand is overcome by central reflexes. Is this inhibition of vasoconstriction or active vasodilatation? It seems to us that, if it is considered to be the former, one would have to concede that it is central inhibition of a first order vasoconstriction.

cutaneous injection of histamine.* The phenomenon does not necessarily indicate that the sympathetic vasodilator nerves course in the posterior roots. The evidence that we have indicates that capillary dilator fibers course in the anterior roots.

Crawford[23] pointed out that the evidence for the existence of vasodilator nerves to the capillaries of the skin is much less certain than that for vasoconstrictor nerves to the capillaries. He quoted the investigators who believe that capillary vasodilators exist, and gave a good bibliography relevant to the subject of capillary innervation. Crawford himself produced evidence to prove the existence of skin capillary vasoconstrictors. He observed the effects on the ear of the albino rabbit of artificially stimuating the cervical sympathetic nerves. The result was always contraction of the capillary.†

Lewis and Landis[24] observed flushing limited to the normally innervated side, after unilateral cervicodorsal ganglionectomy, when the patient was heated. They also observed that emotional blushing was limited to the normally innervated side in such cases. They concluded that emotional blushing required intact sympathetic nerves. They expressed doubt that heat flushing was caused only by an inhibition of vasoconstrictor tone.

The evidence for the existence of active vasodilators to the skin and for the fact that they course in the anterior roots of the thoracolumbar division is drawn from the following observations.

1. We observed that after unilateral cervicodorsal ganglionectomy patients in the heat cabinet occasionally would exhibit a definite capillary flushing on the normal side of the face while the denervated side remained pale. The line of demarcation in the mid-sagittal plane was definite. We found that, if they were heated sufficiently or placed in the inductotherm with or without receiving atropine, the unilateral flushing would always appear. It might be argued that this phenomenon is caused by inhibition of vasoconstriction rather than active dilatation. If this were true, however, one would expect it (flushing on the operated side) to occur after ganglionectomy. We have never observed any semblance of it, although we have watched for it. We have seen it in a mild form on the hands immediately after ganglionectomy. Brown and Adson[25] observed no color changes or demonstrable variations in the capillaries after lumbar ganglionectomy on nonvasospastic patients.

*We have studied the histamine reaction in many patients after preganglionic sympathectomy, after postganglionic sympathectomy before and after degeneration was complete, after extensive anterior rhizotomy and posterior rhizotomy, and the two combined, early and late following operation, after complete transverse lesions of the cord, and after spinal anesthetics. We found normal flares and wheals in all of these cases. The only lesion we did not have was a complete degeneration of a somatic sensory nerve. It is known that the histamine reaction is absent after complete degeneration of a peripheral nerve, and hence the deduction that the phenomenon is an axon reflex of a somatic sensory nerve. We have not reported this study because it confirms only the known facts.

†Since there is such strong evidence for the existence of two types of fibers in the thoracolumbar sympathetic system, one is handicapped in drawing rigorous conclusions from the results of artificially stimulating sympathetic nerves. We have shown that the integrated response to severe heating (this paper) and to severe cooling[20] is capillary dilatation. Transient blanching precedes dilatation in the latter case.

They stated: "There has not been evidence in any case of this series, at least with the methods available, to indicate that capillary dilatation follows interruption of the vasomotor nerves." On one occasion the flushing was present on the normal side during ether anesthesia in one of our patients with a Horner's syndrome caused by Hodgkin's disease. The pathologic side remained pale.

2. After the injection of pilocarpine (gr. $\frac{1}{5}$), we observed this flushing on the denervated side in one case. It was mild, but definite. We do not have evidence that arterioles become sensitized to pilocarpine after ganglionectomy, and this phenomenon occurred in only one case. We do believe that in this instance the pilocarpine acted peripherally, that the capillaries were more sensitive on the denervated side, and that this caused the unilateral flushing.

3. It may be argued that the flushing is due to release of acetylcholine in the tissues as a result of heating. The inhibition of sweat end plates by atropine would help to rule out the possibility that these were a source of acetylcholine, and, in addition, atropine should be able to neutralize any acetylcholine that might be liberated.

It is recognized that, although small amounts of acetylcholine cause capillary dilatation, larger amounts may cause constriction. Hence it may be supposed that, after postganglionic fibers have degenerated, the capillaries become sensitized, so that an amount of acetylcholine which will cause dilatation on the normal side will cause constriction on the denervated side. We feel that the results in the case of Leah C. (Experiment 8) refute this criticism and establish the phenomenon as one of centrally controlled capillary dilatation. In this case the anterior and posterior spinal roots from T 1 to T 5, inclusive, on both sides were severed. In addition to this, a cervicodorsal ganglionectomy was done later on the right. The sweat test demonstrated absence of sweating on the entire face and on the right upper extremity. Therefore, she had a preganglionic sympathectomy affecting the left side of the face, and a postganglionic sympathectomy affecting the right side of the face and right upper extremity. The inductotherm, plus atropine, caused no flushing whatever on the face, but the left hand was flushed and the right was pale.

If this evidence for the existence of capillary vasodilators be accepted, do they course through the anterior roots, as do other efferent sympathetics, or do they reside in the posterior roots? We believe that the following evidence indicates that they are contained in the anterior and not in the posterior roots.

Mabel R. (Experiment 6) had had the posterior roots, only, severed from C 8 to T 4, inclusive, on both sides. Later a cervicodorsal ganglionectomy was done on the right. The heating test brought out good flushing on the left side of the face and none on the right.

One patient who had the posterior roots severed from T 1 to T 10, inclusive, on both sides, showed marked flushing of the face, chest, and arms in the inductotherm while under the influence of atropine (flushing is not as evident below the chest unless the two sides differ for comparison).

It is of interest that one patient, after triple ligation of the left common carotid artery with silk, exhibited marked flushing on the face during the heat test (dry heat only), and that there was no difference on the two sides.

EFFECT OF HEATING ON PULSE RATE AND BLOOD PRESSURE

The pulse rate at the end of the heating experiment was markedly increased, often to twice its previous rate. The blood pressure was usually somewhat decreased, and especially so in cases of essential hypertension (Experiments 7 and 8).

CONCLUSIONS

1. The fingers and toes exhibit the greatest rise in temperature when the body is heated.

2. After unilateral sympathectomy the skin temperature of the fingers or toes will be about equal on the two sides at the end of a heating experiment of the type herein described, regardless of their previous difference, provided these parts were contained in the heating cabinet.

3. Therefore, a sympathectomized arteriole of the skin is capable of dilating as a result of the effect of heat on the vessel itself.

4. Capillary dilator fibers, which are probably a part of a general vasodilator mechanism, supply the vessels of the skin and are centrally controlled. These fibers course through the anterior roots of the thoracolumbar nerves, and thence through the sympathetic ganglia.

5. Since sympathectomy results in a significant rise in skin temperature in only the carpal and pedal extremities, it is logical to deduce that, at room temperatures, the sympathetics do not have much of a constricting effect on the skin vessels except those of the hands and feet.

6. Body temperature under ordinary and average conditions, so far as the skin is concerned, is no doubt maintained largely by responses of the vessels themselves to external stimuli. The central mechanism functions (a) as a governor over the peripheral mechanism, and hence manifests itself more strongly when the need is extreme, and (b) as a mechanism for utilizing or integrating the entire skin surface for heat conservation or dissipation when only a part is subjected to a changing temperature. (These facts will be made more evident in subsequent resports.)

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SPINAL CORD ISCHEMIA IN DISSECTING AORTIC ANEURYSM

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SUDDEN, severe, sustained chest pain, with or without radiation, is often caused by coronary disease. So well did Herrick[1, 2] impress this fact upon the profession that surgeons, as well as internists, at times overdiagnose coronary occlusion, and fail to consider other important conditions with an overriding symptomatology. Hamman[3, 4] ably discussed these entities, including pericarditis, mediastinal emphysema, pulmonary embolism, and esophageal hiatus herniation, and he conspicuously mentioned aortic aneurysmal dissection. Most of his discussion concerned the chest.

The subject of dissecting aneurysm of the aorta is well covered in the literature. Crowell[5] wrote a comprehensive review. From his culling of forty references one learns that the disease has been recognized for nearly a century and a half. Crowell's material consisted chiefly of LeCount's autopsy cases. A consideration of the anatomic observations, therefore, predominates. The article does not lack clinical influence, however, as this excerpt amply testifies: "Very little attention has been paid to the interference with the circulation in the branches of the aorta caused by the splitting of the walls at the places where such branches have their mouths; and it may be safely assumed that the failure to recognize dissecting aneurysms of the aorta during life is at least in part due to failure to appreciate the fact that symptoms of this condition may be produced by interference with the blood supply in these branches. Only a few of the reports examined refer to the amount of the circumference of the aorta dissected at different distances in its length, or to the location of such circumferential splitting." It is evident that this is still true and that more correct ante-mortem diagnoses would have been made if clinicians had been aware of this diagnostic fact.

Holland and Bayley[6] have reported nineteen additional cases of dissecting aneurysm. They reviewed with especial care the theories concerning the cause of the initial intimal tears and the ultimate circular and linear extensions. Their cases illustrate, as do ours, the decided tendency toward rupture into the pericardial cavity (eight cases), and into either the left pleural cavity (four cases) or the mediastinal tissues (four cases). In one instance there were dissection and hemorrhage into both the left pleural cavity and the mediastinum. However, only in connection with Case 12 did the authors make any comment concerning neurological changes in the legs. The 38-year-old woman

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"four days previously," they stated, "had been seized with a sudden excruciating pain in the chest which gradually extended to the toes. Later there was impairment of motion in the lower extremities, which became numb and cold." They mentioned further that thrombi were found in the pulmonic, splenic, and superior mesenteric arteries; and evidently enough heat was applied to the extremities to cause some damage to the skin. This might imply that the attendant suspected occlusion of the vessels supplying the legs; this was not found at autopsy.

Shennan[7] was able to find in the literature only six bona fide cases in which the correct diagnosis was made during life. When Rogers[8] made his report, he was able to collect four additional cases in which the diagnosis had been made and added three of his own. Rogers' article gave us our first appreciation of the relationship between aortic wall dissection and sensory changes or motor paralyses of the legs incidental to sudden interruption of an important portion of the collateral blood supply to the cord. This follows a pinching off or obliteration of segmental (intercostal and lumbar) arteries which arise from the descending and abdominal aorta. These important vessels bilaterally augment the vertebral arterial blood supply (coming down from above) through the pia mater of the cord.*

We have chanced upon a series of these dissections, in which there were lower extremity symptoms, within a comparatively short period. We have asked ourselves, "Why is it that these signs have not been encountered before in cases of aortic wall dissection?" We have put this question to men who have had much experience with cardiovascular disease. It seems to have been the rule to pay little attention to the lower portion of the body, perhaps because attention was focused upon an acutely ill patient afflicted with gripping and tearing pain who died shortly after he was first seen. Nevertheless, not all of these patients die immediately. Rogers reported one man who lived twenty-seven months. A woman whose aneurysm was correctly diagnosed by one of us (E. L. T.) during life lived just short of three months. Hirschboeck and Boman[9] reported the case of a man who survived for nearly four months after a crushing attack and an extensive dissection within the thorax; rupture into the left pleural cavity ultimately occurred. In Case 5 of Hamman's series, the patient lived approximately sixteen months. Under many circumstances there must be sufficient time and opportunity not only to study the lower portions of the body carefully, but in instances of earlier demise to tell the pathologist what is suspected. He may then go farther than "determine the cause of death," and make a more careful examination of the aortic arterial branches which are interrupted at their ostia, as well as examine and appraise the degrees of damage or integrity of the cells of the spinal cord.

*Since the article by Rogers adequately outlines and explains this situation, and since his deductions and experiences so fully coincide with our own, we feel that it is unnecessary to indulge in repetition.

We regret that there was no autopsy in one of our cases. We are reporting in detail one illustrative case. The other reports are abridged. The comparative features are commented upon.

CASE 1.—A married man, aged 54, was employed as an engineer. Four days previous to entering St. Mary's Hospital, he complained of a moderately severe pain in his lower back. This gradually progressed upward and into his chest. He likened it to a pleuritic pain because it was increased on inspiration. At noon, on Feb. 5, 1940, after hanging a fairly heavy door, he had a feeling in the abdomen as if he should go to stool. He did so, but, in attempting to get up, found he could not use his legs. Fellow workmen assisted him into the ambulance and to the hospital. On the examining table in the emergency room he asked the intern in attendance, "Are my legs on the table or off?" No reflexes could be elicited, and sensation in his legs was gone. While he was being examined he had a severe, sudden pain in the abdomen, and it was noted that he became both dyspneic and cyanotic. However, he asked for and took a few puffs from a cigarette and felt somewhat better. After he had been taken to his room, he became fully conscious and with the abatement of his abdominal pain stated that, although he was aware of his legs, he felt as if they were detached from his body. Two hours later he complained of violent pain in the upper abdomen and in his chest. "He drew up his legs on his abdomen as if in extreme pain," says the intern's notes, "became dyspneic, pulseless, and died."

At necropsy* the heart weighed 610 Gm. There was abundant evidence of extensive arterial decay, associated with hypertensive disease. There was a separation of the coats of the aorta all the way from the aortic bifurcation to the base of the aorta. There was a slitlike tear† in the pericardium, producing an ultimate communication from the inside of the aorta, in its first portion, with the pericardial sac. The pericardium contained 250 c.c. of partially clotted blood. The inner aortic layers could be easily peeled off from the outer, and, especially in the abdominal aorta, there was extensive degeneration, with small intimal defects and some calcium deposit.

This interesting item from the autopsy protocol is quoted because of the bearing it has upon whether the symptoms of paralysis in these cases are the result of ischemia of the spinal cord, or of direct ischemia of the limbs, such as that produced, for example, by a saddle embolus. "The aneurysmal dissection extends downward posteriorly and laterally. At a point just above the aortic bifurcation the intimal layer of the aorta is rolled up near a site of rupture, causing almost complete obstruction of the hypogastric arteries. The intima of the hypogastric arteries is likewise displaced, almost completely obstructing their lumina."

COMMENT

The question of the role played by vascular occlusion in the extremities, relative to that of anoxia of the cord, is not likely to confuse anyone who has observed what happens when embolism, either of the main arteries of the leg or of the saddle type, causes obstruction at the bifurcation. Despite the fact that a definite impediment to blood flow may exist, as in this case, the succession of events and symptoms is decisively

*The autopsies in our cases were done by Dr. George L. Berdez, pathologist at St. Mary's Hospital, Duluth.

†This is a very characteristic site of rupture, and means that there is a particular weakness in the aortic wall at that point, or that it is subject to peculiar hydrostatic trauma because of its position. In this case, as in others, there was considerable leakage under the epicardium and the serosa of the aorta. The indirect opening into the pericardial sac, producing hemopericardium, is not infrequently located at some distance from the rupture of the aorta itself.

and dynamically different. This man did not live long enough to show much change or "vacillation" in either his motor or sensory manifestations. Nevertheless, he was totally unable to move his legs when he was brought to the hospital and had lost all sensation in his legs. Then, just prior to death, he was able not only to comment about perverted sensation in his legs, but to draw them forcibly up against the abdomen. Unfortunately, the cord was not examined at autopsy. Had it been, it is not likely that any gross change would have been found because of the relatively short period of ischemia. With respect to the collateral circulation to the cord directly from the aorta, we must not forget that it may change from hour to hour; it depends not only upon mechanical obstruction, but degree of arterial spasm, as well. This physiologic propensity to spasm which accompanies trauma and pain in various portions of the body is now well understood. In this instance the dissection began within the abdomen, and this emphasizes the impression given by various authors that the initial break may not be within the intima itself, but rather a leak from the vasa vasorum of degenerated tissues and vessels, where the dissection up and down separates the aortic layers before either internal or external rupture.

CASE 2.—Within six weeks of the above experience, one of us (P. G. B.) was called in consultation by Dr. J. W. Ekblad to see a delivery man, aged 40 years. He appeared previously to have been in good health. After a heavy, wet snow in March, 1940, he attempted to put chains on the rear wheels of his truck. This was a difficult task, and rather strenuous pulling and jerking were necessary. He was suddenly seized with a choking sensation and a pain in his throat, with radiation down his back of a "hot, searing character." He rested for a few minutes, then walked about a block and climbed one flight of stairs to the doctor's office, where he collapsed. He was given a hypodermic injection of morphine and brought immediately to St. Mary's Hospital. When he was examined about two hours later, he had lost the sensation in both lower extremities and was unable to use his legs. Associated with this was a loss of sensation, or numbness, which began at a very definite level just above the umbilicus and involved all of the body below that point. On the following day (twenty-four hours after the onset), the patient stated that sensation was gradually returning in the abdomen and thighs and to a lesser degree in the left leg. The paralysis on the left side had almost completely disappeared and on the right side had very materially decreased. The blood pressure was normal. The reflexes were absent on the right side, but there was no change on the left.

The clinical impression was that he had had a hemorrhage into the spinal cord, because of the very definite level at which the sensory response was lost and because of the bilateral paralysis below that level. No detailed neurological examination was made. The man was in fair comfort for the next twenty-four hours, when he suddenly died. Before the autopsy one of us (E. L. T.) made the statement that, in view of our previous experience, nothing but dissecting aneurysm could account for his symptoms and signs; and thus, we may say that (belatedly) a correct diagnosis was made before the autopsy, if not before death.

The autopsy findings were almost the same as in Case 1. In this instance the heart weighed 400 Gm.; the evidence of arterial degeneration was not nearly so marked. The dissection had extended just above the aortic valves and down to the bifurcation of the right iliac artery. The dissection was more marked on the right

than on the left side; this was in keeping with the symptoms. A cross section of the right common iliac artery showed that the intimal layer was separated sufficiently to close the vessel almost completely. The mouths of the intercostal and lumbar arteries on the right side of the aorta were torn partially or separated. The aneurysm had ruptured into the pericardial sac, which contained 700 c.c. of blood.

COMMENT

This man, who was sixteen years younger than our first patient and showed much less evidence of hypertensive disease, nevertheless had arterial weakness which, under great strain, was sufficient to cause rupture and death. From the standpoint of treatment, of course, the correct diagnosis could not have been of any especial advantage to the victim.

CASE 3.—A divorced man, aged 73 years, was brought to St. Mary's Hospital on Feb. 13, 1940. At 8 A.M. of that day he had had a terrific pain in the lower back and, when he attempted to get up, could not stand on his legs. He entered the hospital at 2 P.M., complaining of a sense of pressure all over the lower abdomen, and pain in his back. At 9 P.M. he had an attack which lasted about an hour, with moderate dyspnea and some cyanosis. Morphine gave relief. During the next two days, and while he was quiet in bed, there was persistent numbness in his legs; he was unable to void and had to be catheterized. On Feb. 17, 1940, the left leg was still numb and was moved with difficulty; the right leg could be drawn up, but it did not feel natural.

One of us (E. L. T.) was called in consultation on Feb. 18, 1940, by Dr. C. E. Vercellini, who had been attending the man for several years. In the previous history there was nothing eventful. Although his blood pressure had varied from time to time, it held an average level of about 160/100. Several blood Wassermann reactions had been negative. The patient seemed to be comfortable but had a dusky color. There was a good pulse in the dorsalis pedis on both sides. Although he could draw his legs up, he stated that they felt very heavy, and he had little desire to attempt to use them in standing. He spoke of little pain, but mentioned feeling "as though there were a covering over the skin." There were no cardiac abnormalities. Since we had presented the post-mortem observations in our Case 1 at our weekly clinicopathologic conference, Dr. Vercellini had made a provisional diagnosis of dissecting aortic aneurysm. The future course was fully in keeping with that diagnosis.

On the morning of February 21 (eight days after entering the hospital), he appeared tired and depressed and complained of a sense of oppression within the chest. At noon the intern was called because the patient had suddenly become cyanotic and pulseless. He died within a few minutes.

COMMENT

We were denied an autopsy, and the diagnostic impression of aortic aneurysmal dissection rests chiefly upon the sudden abdominal pain, with loss of motion and feeling in the legs, upon the gradual improvement and beginning rehabilitation that followed, and upon the sudden demise that may well have been caused by cardiac tamponage.

CASE 4.—One of us (G. L. B.) performed an autopsy upon a man, aged 78 years. Fig. 1 shows a line of automobiles, with one on the wrong side of the road. The blot of oil indicates the force of the collision. The driver of the car on the proper

side of the road foresightedly took this picture, as well as that shown in Fig. 2. The driver of this erratic car is obviously dead. The tight skin and the prominent veins of the hand clearly indicate his age.

Fig. 1.—The car containing the victim shown on the wrong side of the road.

Fig. 2.—The driver of the erratic car.

This was a case of immediate, sudden death. The autopsy showed "fractures of all the ribs from the first to the seventh on the left side, and of the costal cartilages of the second, third, seventh, and eighth ribs on the same side. *There was no hemorrhage* whatever at the site of the fracture. There was also a fracture of the tibia on both sides, likewise without hemorrhage." He died of "rupture of the upper thoracic aorta and beginning dissecting aneurysm. There was extensive hemorrhage into the posterior mediastinum and an accumulation of 200 c.c. of blood in the left pleural cavity."

COMMENT

Without a necropsy, or the collateral evidence of the car wandering across to the opposite traffic lane, this death would have been attributed to the crushing chest injury, although, as a matter of fact, the man was dead from aortic rupture and mediastinal hemorrhage before the cars collided.

CASE 5.—One of us (E. L. T.) correctly diagnosed, before death, a previously unreported instance of aortic wall dissection in a woman, aged 67 years. She died May 29, 1933. She had been treated for several years for hypertensive disease. Two and one-half months prior to death she entered St. Mary's Hospital with an acute, sudden, crushing pain in the chest which was attributed at the time of onset to coronary thrombosis. However, she developed two signs which were incompatible with uncomplicated coronary thrombosis. After a few days a diastolic murmur appeared at the aortic area. This most certainly had *not* been there before. It was noticed also that a pulsating tumor developed in the upper abdomen, just above the navel. A careful review of the old chart fails to reveal any comment about leg symptoms, except the statement that on entering the hospital she was unable to walk.

The autopsy disclosed the same sort of extensive dissection as in Cases 1 and 2. She had the customary break through the first portion of the aorta within the pericardial reflection. There were 350 c.c. of unclotted blood in the pericardial cavity. The dissection extended downward into the iliacs. Old clots in the outer channel formed the bulge where the upper abdominal tumor had been palpated. *The aortic valves and ring were intact.*

COMMENT

When chest and upper abdominal symptoms predominate, a suddenly appearing diastolic murmur is as diagnostic of supraortic ring dissection as "wandering" paralyses and anesthesia in the legs are of lower aortic wall dissection. Galbraith and Hardwick[10] discussed this feature fully in an excellent case report. They mentioned the reports and opinions of Hamman and Apperly, as well as those of Resnik and Keefer,[11] and favored the latter's explanation and that attributed to Letulle[12]; namely, that "the signs can be accounted for by the ebb and flow from the aorta into the aneurysmal pouch." This implies, and is in keeping with our inference, that the ultimate pericardial sac flooding is a terminal event.

The question remains whether thoracic aortic wall dissection could interfere with either brain or cervical cord circulation sufficiently to cause interruption of nerve impulses to the face or the upper extremities. On theoretical grounds it would appear unlikely that such interruptions could easily produce symptoms comparable to those which occur in the legs. With the exception of certain embolic phenomena, vascular accidents in the upper area rarely are seen. However, our most recent experience is presented for what it may be worth.

CASE 6.—A widow, aged 82 years, died suddenly on April 22, 1940. One of us (P. G. B.) had attended her at his office and at her home over a period of twelve years. Her blood pressure had ranged well above 200/120 for about five years. She

showed unmistakable evidence of cerebral arteriosclerosis. She developed food idiosyncrasies and complained of obstipation. On the morning of the day she died she complained, after straining at stool, of some fleeting dizziness. This passed off, but she remained quite weak and drowsy and slept several hours during the day. In the late afternoon the daughter noticed that she had difficulty with her speech, and there appeared to be a weakness or paralysis of the right side of the face. This lasted for only about an hour, at which time the patient felt better and seemed to be recovering. The family left her for a short time during dinner, and, when they returned, she was dead.

Autopsy revealed advanced arteriosclerotic changes within the aorta, and there was a moderate-sized aneurysm of the left common iliac artery. An aneurysmal dissection was beginning just above the aortic ring, with the same type of opening into the pericardial sac as in the other cases. The pericardium contained 840 c.c. of blood, and there was a bilateral hydrothorax.

COMMENT

It is doubtful whether anything which happened to this woman should be attributed to a neurological lesion incidental to this particular dissection. Any lay person is well enough qualified to judge of speech difficulties, but lay ideas about facial paralysis are very prone to be faulty. Nevertheless, this experience is at least suggestive. The autopsy protocol states: "A dissecting aneurysm of the aorta extends up to the horizontal part of the arch of the aorta." As pointed out by Crowell, there is need for more careful measurement of the mouths of the greater and lesser arteries which come off where aneurysmal dissection begins. Partial or complete closure of the great vessels to the head could produce cerebral ischemia readily.

SUMMARY AND CONCLUSIONS

1. Six cases of dissecting aortic aneurysm are reported, in five of which the diagnosis was confirmed at autopsy. In two instances it was possible to make a correct diagnosis before autopsy.

2. Wandering paralysis and vacillating sensory disturbances below the level of the umbilicus are stressed as very important diagnostic signs.

3. Spinal cord ischemia caused by interruption of an important source of blood supply directly from the aorta is discussed.

ADDENDUM

Among the articles which have appeared since this paper was submitted for publication, the following from the Massachusetts General Hospital[13] deserves comment.

A 57-year-old woman with hypertension, four hours after sensation of smothering, showed "a gradually increasing pain and tingling in her right leg, soon followed by numbness, coldness, and paralysis of this extremity." There was "transient tingling in the right foot." Surgical search for an embolus in the subpoupart portion of the right femoral artery was unsuccessful. The divided femoral vein bled freely from

above. At necropsy, aneurysmal dissection of the same type we have described was found to extend from a few centimeters above the aortic ring to the right external iliac, and 5 cm. above Poupart's ligament, where a fold of the intimal surfaces such as we have observed seemed to occlude the lumen.

The discussion by the clinicians failed to mention the paralytic symptoms, and they did not comment on the fact that "Two and a half hours after admission the patient could move her ankle but not the toes." We infer that the neurogenic factor was not considered.

Toomey[14] has recently discussed the "segmental" character of the paretic and paralytic phenomena in poliomyelitis. His observations help explain both the vacillation and degree of the paralysis which we are discussing. He says, "Fibres from several segments run from the cord to several muscles in the periphery often in one large nerve." Thus he explains why there will be especial selectivity in the muscle groups afflicted; some from the same nerve will remain intact. The same factor seems to obtain in the segmental nutritional failure after aortic wall dissection.

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THE EFFECT OF CHRONIC CARDIAC COMPRESSION ON THE SIZE OF THE HEART MUSCLE FIBERS

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INTRODUCTION

CONSIDERABLE confusion exists concerning the status of the heart in the compression disorders (Pick's disease, constrictive pericarditis). Is the compressed heart of normal size, is it smaller than normal, or is it larger than normal? Is the pull upon adhesions a factor in producing failure of the heart? Should the pectoral muscle and bony precordium be removed as a separate and distinct part of the operation for the cure of Pick's disease? Such a prominent surgeon as Schmieden[1] recommended removal of the pectoral muscle and the bony precordium, together with excision of the adherent scar. Schmieden's view was supported by Sauerbruch,[2] Winkelbauer,[3] Westermann,[4] Volhard,[5] and Fischer.[6] Throughout the literature on this subject it is stated that adhesions disturb the circulation. To relieve the ill effects of adhesions to the diaphragm, Payne, Sauerbruch, Fischer, and Schmieden recommend that the diaphragm be paralyzed by cutting the phrenic nerve. As a result of experimental studies, Ochsner and Herrmann[7] and Herrmann and Musser[8] concluded that adhesive pericarditis embarrassed the heart. According to these investigators, adhesions produce enlargement and hypertrophy of the heart. The terms used to designate these disorders—Pick's disease, Concato's disease, adhesive pericarditis, constrictive pericarditis—do not add clarity to the subject. This is readily apparent in discussions on diagnosis. It would appear that we are dealing with two factors which produce circulatory failure, namely, compression and a pull on adhesions.

The Pick syndrome was produced experimentally for the first time by Beck,[9] in 1928. The development of the syndrome was incidental to a study of the action of a surgical solution of chlorinated soda (Dakin's solution) in the pericardial cavity. The study was undertaken to ascertain whether or not this solution could be used safely in the treatment of purulent pericarditis. After it was noted that cardiac adhesions and ascites followed the application of this solution to the pericardial cavity, it became apparent that a method was at hand to produce the Pick syndrome in animals. Beck and Griswold,[10] using this method,

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carried out a study in which two observations of some importance to our subject and not in the literature at that time were made. One was that the Pick syndrome could be produced without any cardiac adhesions. The other was that, when the Pick syndrome developed, the heart became smaller than normal and that, when the pericardial scar was excised, the heart subsequently became of normal size. These measurements were made on standardized roentgenograms of the heart. The scar around the heart adds a certain amount to the roentgenographic shadow, and it is sometimes impossible to ascertain the size of the heart with any degree of precision because one cannot tell what part is scar and what part is heart. Because of this it is stated by several authors that the heart in this disorder can be small, normal, or large. In an analysis of the roentgenograms of twenty-six of our patients with compression caused by scars, Freedman[11] found that the cardiopericardial shadow was normal in size or smaller than normal in eighteen cases, moderately enlarged in six, and greatly enlarged in two. The heart shadow and the cardiopericardial shadow in this disease are not the same thing. It may be difficult or impossible to ascertain the exact weights of the hearts of patients who die from pericardial disease because the scar must be dissected from the heart before the organ is weighed. We know of no data on this subject, and a ratio between heart weight and body weight cannot be given. Even if such data were available, the patient's edema would disturb the ratio.

Fortunately the presence of atrophy or hypertrophy of the heart can be established by measurements of individual muscle fibers without knowing the exact weight of the heart. There is a perfect, positive, straight-line correlation between the size of the heart and the diameter of the fibers. This exact correlation (correlation coefficient = plus 0.872 [± 0.019]) was discovered by Roberts and Wearn[12] in a recent study of the capillary supply of the human heart during hypertrophy and growth. A similar study was carried out on rabbits by Shipley, Shipley, and Wearn.[13] The method of these workers was used in the investigation reported here.

MEASUREMENTS

Five human hearts were available for study. Each of the patients from whom the specimens were obtained had had a severe degree of cardiac failure, presumably as a result of pericardial disease. In each case the heart was everywhere adherent to the pericardium. The pericardium was thickened, and was adherent to the diaphragm, pleurae, and chest wall. These patients died after removal of the scar. The heart weights given are those which were obtained after careful resection of the scarred pericardium (Table I).

Four sections were taken from various regions of the right and left ventricles of each heart, and 100 adjacent fibers were measured in each

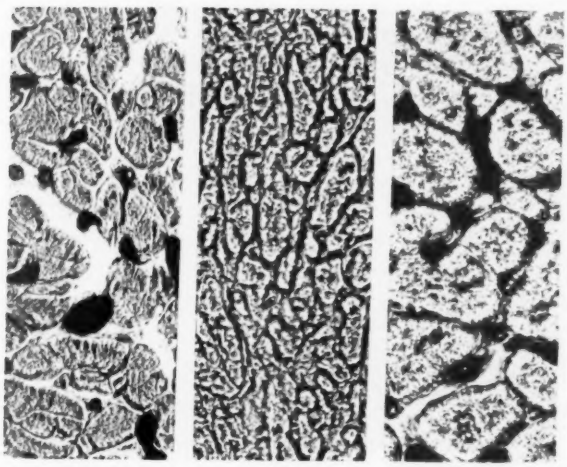
section. Two diameters of each transversely cut fiber were measured with a calibrated ocular micrometer. In Fig. 1 the small muscle fibers of a compressed human heart are contrasted with the fibers of a normal and a hypertrophied heart. The mean fiber diameters in the five human hearts were 8.1, 8.9, 10.1, 11.2, and 11.2 microns. The average of the five mean measurements was 9.9 microns. In a study of twenty-six adult, normal, human hearts Roberts and Wearn[13] found that the average mean fiber diameter was 13.9 (± 0.18) microns. The methods of measurement were the same in both studies. It can be seen that the largest fiber diameter in the group of five hearts from cases of pericardial disease and cardiac failure was less than the average normal. The average reduction in fiber diameter in the group of compressed hearts was 27.2 per cent of the normal value. The mean fiber diameter and the heart weights in these five cases of pericardial compression are plotted against each other in Fig. 2. This is a reproduction of the graph showing a positive correlation between heart weight and fiber diameter in children's and adults' hearts, taken from the paper of Roberts and Wearn,[12] with the addition of these five compressed hearts.*

TABLE I

CASE	FIBER DIAMETER (μ)	HEART WEIGHT (GM.)	HEART WEIGHT: BODY WEIGHT
Human			
1	8.1	175	0.00530
2	8.9	210	0.00295
3	10.1	360	0.00465
4	11.2	240	0.00381
5	11.2	280	0.00538
Av.	9.9	253	0.00442
Normal (Roberts and Wearn)	13.9 (±0.18)	311 (±7.42)	0.00543
Dog			
1	11.8	80	0.00666
2	12.6	75	0.00577
3	14.5	84	0.00600
Av.	12.9	80	0.00614
Normal (Mean of 6)	18.5	128	0.00827

An experimental study was made on eleven dogs. Constricting bands of linen tape were placed around the heart on the outside of the parietal pericardium. In several experiments the tapes were tightened at repeated operations at intervals of several months. In three of the experiments severe circulatory failure developed slowly over a period of about a year. The signs of circulatory failure consisted of ascites, high pressure in the jugular veins, subcutaneous edema, enlargement and frosting of the liver, distant heart sounds, and reduction

*In the graph these five compressed hearts are seen to fall well below the probable error of values for heart weight as predicted from the regression line (middle line) correlating heart weight and fiber diameter; this line, determined by Roberts and Wearn, has the formula: Fiber diameter ± 1.51 μ = 8.22 + (0.0199 × heart weight).



A. *B.* *C.*

Fig. 1.—Photomicrographs of transversely sectioned, adult, human, cardiac muscle fibers. *A*, Normal; *B*, compressed heart of adhesive pericarditis; *C*, hypertrophied heart of syphilitic aortic insufficiency (×500).

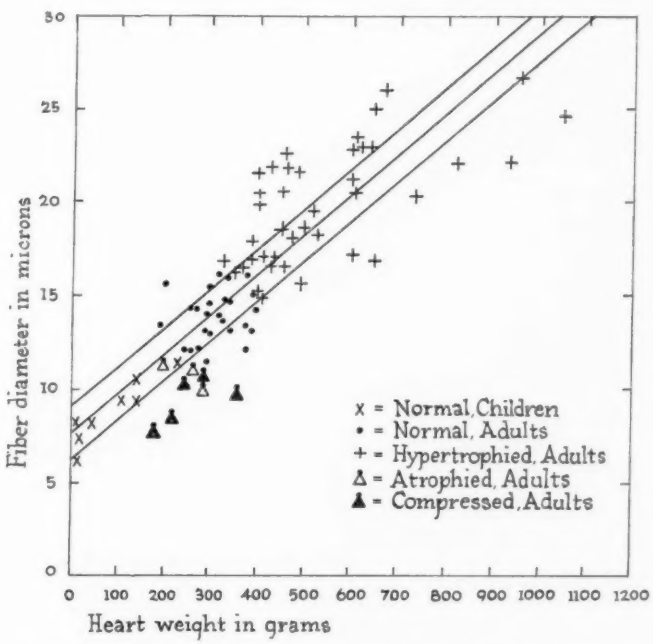


Fig. 2.—Chart correlating the heart weight and fiber diameter (human). The five hearts which had been chronically compressed by pericardial adhesions were smaller and had smaller fibers than the normal hearts studied by Roberts and Wearn.[12] The middle line is the repression line for fiber diameter from heart weight, and the upper and lower lines represent the range of the probable error for predicted values, as determined for the other noncompressed hearts shown here.

in the amplitude of the pulsations of the heart. When these animals were sacrificed, the tapes were found to be compressing the ventricles. Adhesions to the pleurae and mediastinum obscured the tapes. There were also some adhesions between the heart and parietal pericardium. The mean fiber diameters in these three dog hearts were 11.8, 12.6, and 14.5 microns. The average was 12.9 microns. A similar study on six normal, adult, dog hearts showed that the mean diameter was 18.5 microns. According to these measurements, the fiber diameter was reduced by about 30 per cent of the normal value. Table I summarizes the results of the study.

In both the human hearts and the experimental specimens there was a marked tendency toward uniformity in the size of the small fibers. This is in agreement with the observations of Karsner, Saphir, and Todd,[14] who found that in the cardiac atrophy of chronic wasting disease the variability in fiber size which is characteristic of the normal heart is replaced by a uniform diminution in the size of the larger fibers. Also, the small fibers tended to be circular in cross section, rather than somewhat elliptical.

COMMENT

Each heart in which the fiber diameters were measured was compressed over a period of months or years. Adhesions between the heart and pericardium and between the pericardium and diaphragm, pleurae, and chest wall were present. Every specimen showed atrophy of the muscle fibers, and none showed hypertrophy of the muscle fibers. The presence of atrophy and the absence of hypertrophy in the individual muscle fibers signifies the presence of atrophy and the absence of hypertrophy in the entire heart. It appears, then, that cardiac compression produces cardiac atrophy and that adhesions do not produce hypertrophy of the compressed heart. According to the observations of Hosler and Williams,[15] adhesions do not produce hypertrophy of the heart in the absence of valvular disease or hypertension, either in experimental animals or in human beings.

If the results of this study can be applied to compressed hearts in general, we can say that adhesions that do not compress the heart can be disregarded as a possible cause of failure in cases of compression. We can say also that there is no indication for removing the bony precordium or for paralyzing the diaphragm in the surgical treatment of this condition. That this conclusion is correct is demonstrated by the results of operations on patients with compression. Thirty-seven patients were operated upon by Beck. These patients had cardiac compression, together with adhesions to the chest wall, diaphragm, pleurae, pericardium, and heart. The compression scar was dissected from the heart and excised. As little of the bony precordium was removed as possible. The pectoral muscle was not removed, and the

diaphragm was not paralyzed. Of these thirty-seven patients, twenty-five were completely free from ascites after the operation and may be regarded as cured. Two additional patients were improved, and seven died. Of the two patients who were only improved, one had invasion of the myocardium by the scar, so that the heart was the seat of both extrinsic and intrinsic disease, and a complete cure could not be expected. The other had reformation of calcium deposits around and in the myocardium. Of the seven patients who died, three had active tuberculosis of the pleurae and mediastinum, one had an epicardial scar, plus bloody fluid, and died of infection, two died of heart failure caused by acute dilatation of the atrophic heart, and one died of ventricular fibrillation during the operation. It is obvious that removing part of the chest wall and paralyzing the diaphragm could not improve these results.

That the compressed heart undergoes atrophy of disuse was demonstrated by the clinical course of many of these patients. In every instance the heart dilated as the scar was removed. In every instance the circulation showed immediate improvement. Not infrequently, however, some of the improvement was lost after a day or two. The subsequent improvement in many cases was gradual, extending over a period of weeks or months. This delay occurs, we think, because the recovery from the atrophy of disuse suffered by the heart muscle is gradual. One would expect the heart muscle to require as much time as skeletal muscle to recover from an atrophic state.

CONCLUSIONS

1. In a series of human and dog hearts that were chronically compressed, the muscle fibers were smaller than normal in each instance.

2. In the presence of cardiac compression there is no evidence to indicate that adhesions play any role in producing circulatory failure, and there is no evidence to justify operation on the bony precordium, pectoral muscle, or phrenic nerve of patients with adherent and compressed hearts.

3. The compressed heart undergoes atrophy of disuse.

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ERRORS IN MEASUREMENT OF THE P-R (P-Q) INTERVAL AND QRS DURATION IN THE ELECTROCARDIOGRAM

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IN THE fall of 1938, two interesting cases which were encountered within a brief period of time called our attention to a common and significant error in the measurement of the P-R (P-Q) interval of the electrocardiogram that has as yet escaped notice in the literature except for a brief preliminary reference published by us in the Transactions of the American Society for Clinical Investigation for 1939.[1] Fuller details and a further study of this problem are presented herewith.

It has been long recognized that the P-R interval and QRS duration are not always uniform throughout all leads of the electrocardiogram. In any given instance it is known that not all leads are equally favorable for recording the various deflections. The P waves are often poorly marked in Leads I and III, and the QRS complexes, particularly in Lead III, are subject to considerable variation in form. Lead II, which represents the algebraic sum of Leads I and III, usually has well-marked deflections, and it has been used most often for measurements of the time intervals.

Possible reasons for a variation in time intervals have been inadequately studied, and in books on electrocardiography one finds little definite reference to methods of measuring these intervals. Many books do not discuss the matter at all, except to state that the P-R interval is that portion of the tracing from the beginning of the P wave to the beginning of the QRS complex. In most cases there is no statement regarding lack of uniformity in different leads. Vaquez and Laidlaw[2] do not say how the P-R interval should be measured, but give the normal duration as 0.15 to 0.18 second. Lewis[3] says that the measurement should be made from the beginning of P to the beginning of the ventricular complex, and that, as a rule, R is chosen for the sake of uniformity, but Q may be used if it is thought desirable. Carter[4] recommends measuring from the beginning of the P wave to the beginning of the first deflection of the QRS, whether the latter is an upstroke or a downstroke. He further states that all measurements of complexes should be made in the lead in which they are longest, which is usually Lead II, but that sometimes Lead I or Lead III gives information not available elsewhere. Pardee[5] also mentions the variation in the recording of P and QRS, but states that the longest P-R interval in any lead will be the most nearly correct one. Ashman and Hull[6] say that the QRS

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should be measured in the lead in which it is widest. They do not, however, discuss the mechanism of its variation.

It had been our practice in the routine reading of electrocardiograms to accept the longest intervals for P-R and QRS as the correct ones in any given record. The two cases already referred to in the first paragraph of this paper indicated, however, the need for further study and standardization of measurements in electrocardiography. The first patient, a healthy man, aged 52 years, had applied for insurance and showed no abnormalities on examination except for a P-R interval of 0.21 second in Lead II. Upon close scrutiny it was apparent that the P-R intervals in Leads I and III were both 0.18 second. There was a small Q wave in Lead I and a small R wave in Lead III which just balanced each other in Lead II to make the first part of the QRS complex isoelectric, thus adding 0.03 second to the P-R interval and shortening the QRS complex by the same amount in Lead II. It was obvious in this case that Lead II was unfavorable for measurement of both P-R interval and QRS duration, and also that the longest P-R interval was not the correct one.

A few days later a second case was encountered; this patient was a woman, aged 55 years, with lower chest pain, gaseous distention, and nausea, who was suspected of having coronary disease, despite a negative physical examination, because she had a P-R interval of 0.21 second in Lead II. Scrutiny of Leads I and III, however, disclosed, as in the first case, P-R intervals within normal limits (0.18 second), with Q_1 balancing, and so neutralizing, R_3 (Fig. 1).

Because these two cases seemed to refute accepted opinions, our interest was aroused concerning the nature of variations in other cases, and in establishing, if possible, criteria for the correct measurement of P-R interval and QRS duration. Records similar to the first two were soon found in the course of routine work in the laboratory, and simultaneous leads were taken in such cases to ascertain definitely the time relationship of the deflections in the various leads. Accurate measurements made with the Lucas comparator confirmed the first impression in these cases, and since the point of variation in the value of P-R intervals and QRS durations was not always the same in each case, a measurement of the P-S duration was instituted as a further aid. Its value will be illustrated later.

It was soon apparent that there are several ways in which the time intervals may vary in the different leads. The balancing of Q_1 and R_3 in cases of left axis deviation (Fig. 1) is a common type. In cases of right axis deviation the reverse occurs, that is, balancing of R_1 and Q_3 (Fig. 2). Apparent shortening of the P-R interval, especially in Lead I, occurs because of the isoelectric beginning of the P wave (Fig. 3), but is of little importance, per se, because it does not influence the other leads. Shortening of the QRS interval alone results in Lead II through

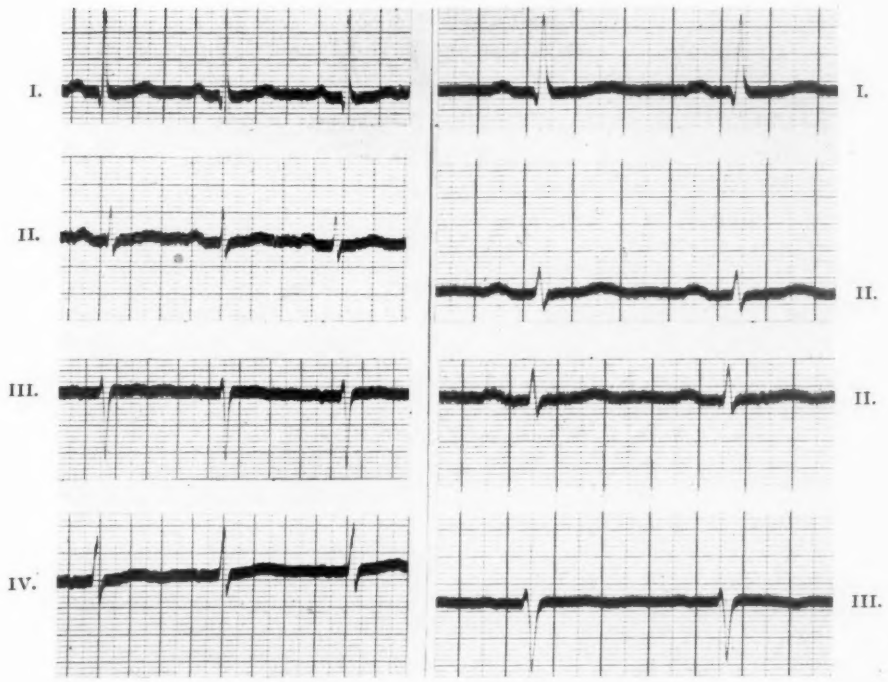

Fig. 1.—*A*. Routine Leads I, II, III, and IV. *B*. Simultaneous records of Leads I and II above, and of Leads II and III below. The small Q_1 and R_3 neutralize each other, to make the start of QRS_2 isoelectric. $P\text{-}R_2$ is longer and QRS_2 shorter than the corresponding intervals in Leads I and III. $P\text{-}R_1 = 0.18$ sec. $P\text{-}R_2 = 0.21$ sec. $P\text{-}R_3 = 0.18$ sec. Time = 0.2 and 0.1 sec. in this and in the following figures.

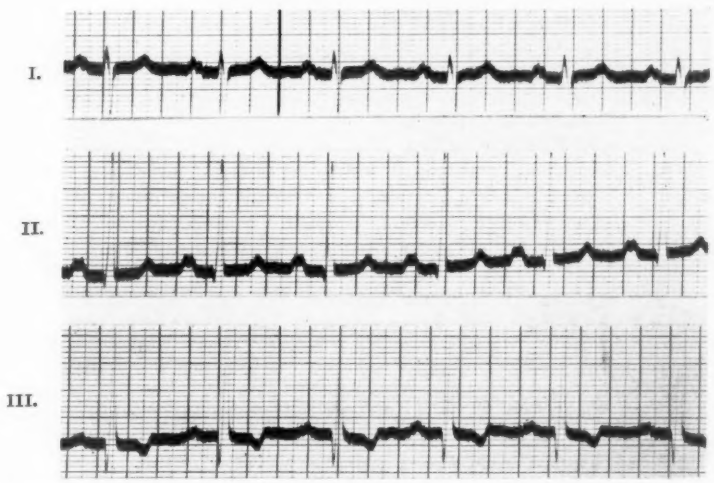

Fig. 2.—Routine Leads I, II, and III. Partial neutralization of R_1 and Q_3 produces an isoelectric beginning of QRS_2. $P\text{-}R_1 = 0.20$ sec. $P\text{-}R_2 = 0.23$ sec. $P\text{-}R_3 = 0.21$ sec. Corresponding decrease in width of QRS_2.

balancing of the S phases in Leads I and III, producing an isoelectric ending of QRS_2 (Figs. 4 and 5). It is seen in Figs. 4 and 5 that abnormal widening of the QRS waves would be overlooked if only Lead II were considered for measurement of the QRS, because the QRS duration is narrowed by isoelectric phases at both beginning and end. Fig. 6 illustrates the value of the P-S measurement. The QRS durations are different in all three of the standard leads, and the P-R interval in Lead I is shortened. The true P-R interval, as judged by the longest P-S duration minus the longest QRS duration, differs from all of the P-R intervals obtained by direct measurement. Apparently QRS in Lead II is narrowed by an isoelectric phase at the start, while QRS_3 is isoelectric at the end, and the P-R interval in Lead I is shortened by a late beginning of P.

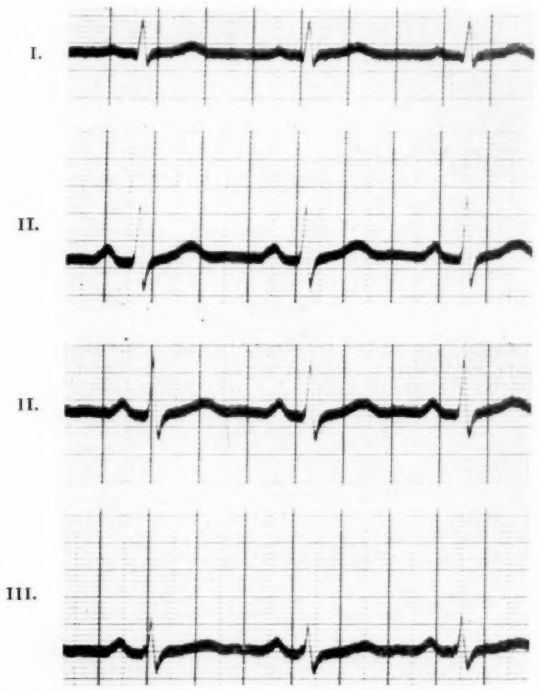

Fig. 3.—Simultaneous records of Leads I and II above, and of Leads II and III below. The isoelectric beginning of the P wave and the isoelectric ending of the QRS complex shorten both the P-R interval and the QRS duration in Lead I.

In order to get some idea of the incidence and possible importance of these variations in the time intervals, the electrocardiograms of 1000 consecutive patients were reviewed. A large number had a shorter P-R interval in Lead I only, and these were eliminated from consideration because, when Leads II and III agree, it is unlikely that any confusion could arise in arriving at the correct values. Thirty-eight tracings (3.8 per cent) were found to show significant variations (0.02 second or

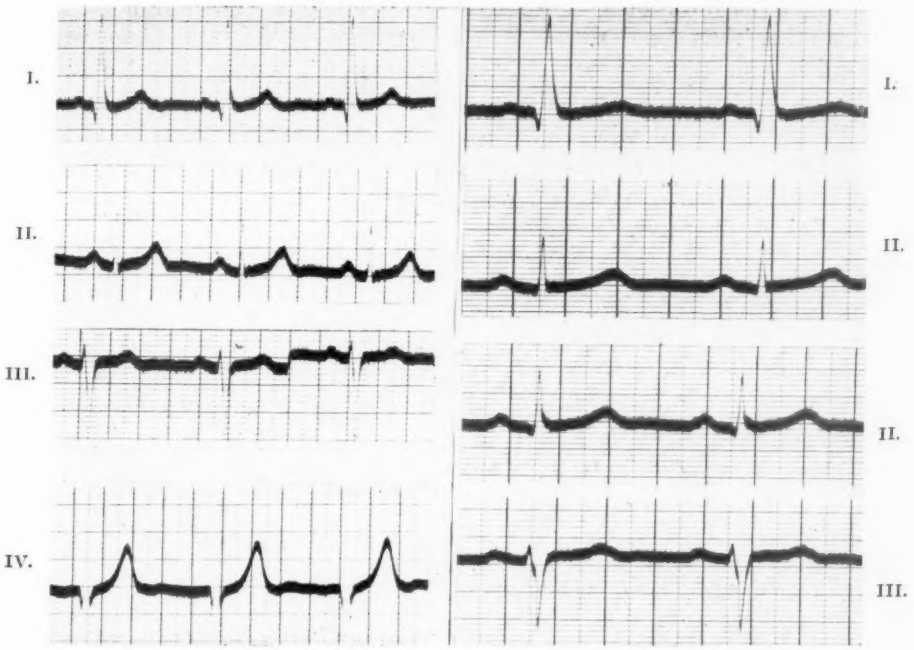

Fig. 4.—*A*. Routine Leads I, II, III, and IV. *B*. Simultaneous Leads I and II above, and Leads II and III below. QRS_2 shows isoelectric beginning and ending. Marked shortening of duration of QRS_2 as compared with these complexes in Leads I and III.

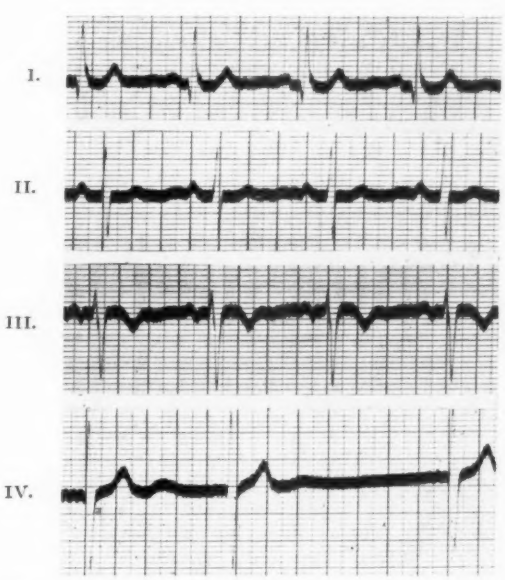

Fig. 5.—Routine Leads I, II, III, and IV. Small Q_1 and R_3 neutralize each other to lengthen the P-R interval and shorten the QRS duration in Lead II by 0.03 sec. The slightly prolonged intraventricular conduction time (0.11 sec. in Leads I and III) is not apparent in Lead II. $QRS_2 = 0.08$ sec.

more) in the duration of the P-R interval or QRS waves, or both, in leads other than Lead I. A variation in the P-R interval alone was found in nine (0.9 per cent). Five patients (0.5 per cent) had differences in the QRS duration only. It was evident that in ten (1 per cent) of the cases the variations were clinically important, in that the short and long intervals straddled the dividing line between normal and abnormal, and because the determination of the correct values influenced the clinical diagnoses.

Fig. 6.—*A*, Routine Leads I, II, III, and IV. *B*, Simultaneous Leads I and II above, and Leads I and III below. Late beginning of P_1, balancing of Q_1 and R_3, and isoelectric ending of QRS_3 make the time intervals differ in all three of the standard leads in the routine tracing (*A*). The true P-R interval, determined from the longest P-S (Lead II) minus the widest QRS (Lead I), equals 0.17 sec. and is different from any of the recorded P-R intervals. *B*, taken at a later date, illustrates well the isoelectric ending of QRS_3.

The most common mechanism responsible for the disagreement between different leads was the balancing of Q_1 and R_3 in cases of left axis deviation (thirty-one instances). The balancing of R_1 and Q_3 was responsible in only three cases. Thirteen tracings showed isoelectric S phases, and four records had shortened P-R intervals in Lead III because the beginning of the P waves was isoelectric. In eighteen cases there was poor recording of the beginning of P_1; this was an incidental observation in this group.

Of the thirty-three cases in which there were variations in the P-R intervals, the longest P-R interval was incorrect in twenty-six and correct in seven. Lead II showed the correct P-R interval only six times

in this group of thirty-three patients. In four instances the correct P-R interval, as ascertained from the P-S duration minus the longest QRS duration, differed from all of the recorded intervals. It is obvious that the QRS duration can err in only one direction, and that the longest one recorded must be most nearly correct. Contrary to the literature, however, Lead II did not prove to be the most reliable for this measurement. Of the twenty-nine patients with significant variations in QRS duration, with or without P-R interval discrepancies, not a single one had the correct value in Lead II. The apparent narrowing of the QRS waves is produced either by balancing of Q and R in Leads I and III, or by balancing of S phases, and this invariably affects Lead II, making the QRS complex narrower than it should be. It has already been shown (Figs. 4 and 5) to what extent this narrowing can occur.

Simultaneous registration of two leads affords the proof of these observations. However, in the absence of facilities for such registration it is still possible to decide with reasonable accuracy what are the correct P-R interval and QRS duration. At a glance it is evident whether Q_1 and R_3 or R_1 and Q_3 are about equal in amplitude and duration, whether the P is small and late, as it frequently is in Lead I, making the P-R interval too short in that lead, and whether the QRS is too narrow in one or more of the leads. One may obtain an approximately accurate P-R interval, without taking simultaneous leads, by subtracting the figure for the widest QRS wave from the longest P-S duration (that is, from the beginning of P to the end of S). In doubtful cases, Lead III is most likely to give the correct P-R interval. We have been able to prove the validity of these observations by the registration of simultaneous leads with our double string galvanometer, which has separate connections for each lead. Comparisons of the original tracings with those using simultaneous leads are shown.

The exact clinical significance of the observations reported here cannot be ascertained at once. However, since significant discrepancies in time relations occurred in about 3 per cent of the cases in our series, it is likely that these measurements will be of importance individually in an appreciable number of instances, either from the standpoint of insurance or diagnostically. The question also arises whether or not present standards of normal for P-R interval and QRS duration are actually correct. If normal standards for P-R intervals are based on measurements of the longest one in any lead, it is possible that our present upper normal limit has been fixed too high. We are not prepared to say at present whether an incidence of variation such as we have found would modify existing statistics or not.

Hill,[7, 8] has recently gone back a little further to the fundamentals of differences in time relationships among the various leads in exploring the action currents over the chest wall. He also points out the occur

rence of isoelectric phases in the complexes, with resultant discrepancies in measurements, and recommends observation of the intervals in all leads; he finds that if one P-R is different from the other two, the two that agree are correct, and if all three are different, the intermediate one is correct. Our results agree in most instances with his when we figure them according to his observations. However, we believe that the use of the P-S interval measurement is more reliable, for, in an occasional case (Fig. 6), direct measurement gives incorrect values from all three leads because of the presence of isoelectric phases (four cases in this series).

SUMMARY

1. We have discovered errors in existing methods of measurement of the P-R interval and QRS duration in the electrocardiogram.

2. These errors are usually the result of balancing of similar deflections of opposite direction in Leads I and III, producing isoelectric phases in Lead II. Lead II, therefore, is often the least reliable for the measurement of electrocardiographic time intervals.

3. Such variations were found to occur in 3.8 per cent of 1000 consecutive cases.

4. It is pointed out that the variations may be of considerable individual significance diagnostically, and may be of statistical importance from the standpoint of existing accepted values for normal limits of the P-R interval and QRS duration.

5. A simple method of avoiding the errors is presented. In general, Lead III has been found to be the most reliable single lead for the measurement of time intervals.

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OBSERVATIONS ON REACTIVE HYPEREMIA IN VARIOUS PORTIONS OF THE EXTREMITIES

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IN GENERAL, it can be stated that the functional needs of a tissue largely determine the rate of local blood flow. In any situation in which function is dependent upon local metabolism, it would follow that this latter factor should likewise play a role in controlling the rate of local blood flow. Insofar as the hand and fingers are concerned, however, marked and transient variations in flow have been reported. These variations obviously could not be related to changes in metabolism, and have been attributed, in part, to the fact that the hand, through the medium of its numerous arteriovenous shunts, performs an important function in the conservation and dissipation of body heat under ordinary environmental conditions.[1] Further, it has been shown that the vessels in the hand respond markedly to other types of stimulation.[2-4] Since the transient alterations in flow produced by these various factors are dependent upon the integrity of the sympathetic nervous system,[5] the vascular responses in the sympathectomized hand would be expected to be much more closely related to the metabolic needs of the tissues than are those in the innervated hand; this relationship was demonstrated recently by Freeman.[6]

A number of investigators, notably Bier,[7] Moskowicz,[8] Roy and Brown,[9] Lewis and Grant,[10] and Freeman,[6] have studied the phenomenon of reactive hyperemia, which, in brief, designates the duration of increased blood flow to an extremity after a period of arterial occlusion. Some of these workers feel that, within certain limits, the subsequent increase in circulation is dependent upon the length of time that the tissues suffer from anoxia. According to Roy and Brown,[9] the increased blood flow represents an attempt on the part of tissues which have been deprived of a proper blood supply to become repossessed of it. Since reactive hyperemia appears to be related to tissue metabolism, it was thought worth while to study this response in the innervated hand, in the forearm, and in the leg, in the hope that more information might be gained concerning the mechanism involved in the increased local blood flow in the different vascular beds.

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METHOD

The effect of varying periods of arterial occlusion on blood flow in the hand, forearm, and leg was studied in a series of forty-three normal subjects by means of the venous occlusion plethysmographic method. The sympathectomized extremities of a female patient (R. M.), with Raynaud's disease, were also tested. Generally, from two to five experiments were performed upon each subject. Blood flow readings were made simultaneously on two extremities which were exposed to a bath temperature (temperature of the water in the plethysmograph) of either 10° to 14°, 32°, or 45° C., at a room temperature of 25° to 27° C. In the case of the forearm and leg, pressures of 300 mm. Hg were maintained at the wrist and ankle during the period of blood flow measurements, so that vascular changes in the distal portions of the extremities could not influence the results.[1] The apparatus and technique used in obtaining and calculating the blood flow measurements were similar in all respects to those previously described.[11]

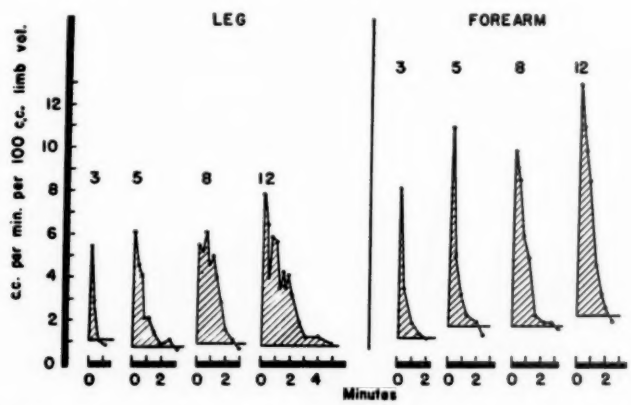

Fig. 1.—Effect of varying periods of arterial occlusion upon magnitude of *total* blood flow repayment. Leg (C. B.)—3 min. occlusion—1.5 c.c. total repayment; 5 min.—4.0 c.c.; 8 min.—6.4 c.c.; 12 min.—10.8 c.c. Forearm (L.S.)—3 min. occlusion—2.7 c.c. total repayment; 5 min.—4.0 c.c.; 8 min.—7.2 c.c.; 12 min.—10.8 c.c. Bath temp.—32° C.

After eight to ten control readings were obtained over a period of twenty to thirty minutes, reactive hyperemia was produced by suddenly applying an arterial occlusion pressure to the proximal portion of the limb by means of a blood pressure cuff connected to a pressure system. In the case of the forearm and hand, the cuff was generally applied to the arm just above the elbow, and of the leg, to the thigh above the knee. In a number of instances, reactive hyperemia was elicited in the hand by applying the cuff around the forearm. After different periods of application, ranging from three to twelve minutes, the pressure was released and blood flow readings were obtained at 10-second intervals for the first two minutes, and then at longer intervals for the next eight minutes. In some instances, the first measurement was recorded within a second after the onset of reactive hyperemia, according to the technique of Lewis and Grant.[10]

For each experiment a graph was constructed from the blood flow measurements (in c.c. per min. per 100 c.c. of limb vol.) which were obtained during the ten-minute interval after the release of the arterial occlusion pressure (Figs. 1 and 2). By means of a planimeter, the number of cubic centimeters of excess blood flow over and above the estimated control level was obtained for the period of reactive hyperemia. The basal flow during reactive hyperemia was ascertained by averaging a number of resting blood flow figures which were obtained before arterial

occlusion and after the effect of the occlusion had disappeared. Since different periods of arterial occlusion were used, it was necessary to express the number of cubic centimeters of excess blood flow as the actual repayment elicited by one minute of arterial occlusion for each 100 c.c. of limb volume. The percentage of blood flow "debt" which was repaid was calculated by dividing the repayment for one minute of occlusion by the theoretical "debt" incurred during this period of time. The latter figure was regarded as equal to the control blood flow per min. per 100 c.c. of limb volume, on the assumption that this quantity of blood would have ordinarily entered the limb during each minute of the experimental period if no occlusion pressure had been applied.

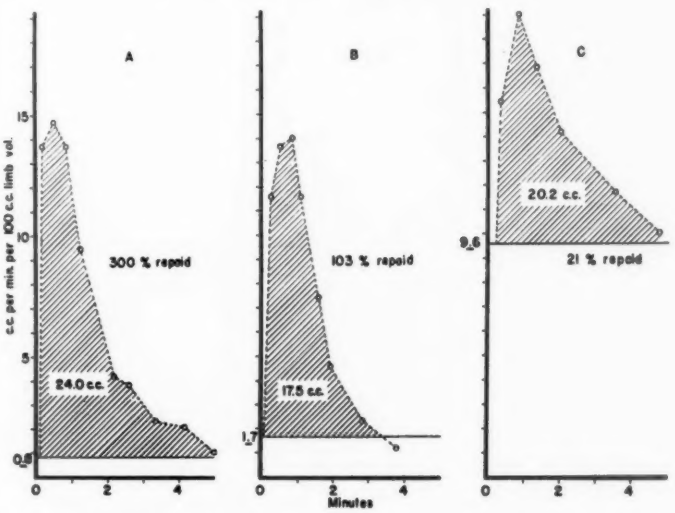

Fig. 2.—Hand. Effect of a ten-min. period of arterial occlusion in subjects J. S. (*A*), H. P. (*B*), and C. W. (*C*), with different control blood flow levels. Figures within graphs—*total* repayment over and above control blood flow levels. Theoretical "debt" incurred calculated by multiplying control blood flow by ten minutes. Bath temp.—32° C.

RESULTS

Comparison of type of response of the hand, forearm, and leg to arterial occlusion.—In the case of all three of these sites, the greatest augmentation of flow at the different bath temperatures took place within the first ninety seconds after removal of the arterial occlusion pressure. From that point on, the flow rapidly and progressively diminished, so that, after a ten-minute occlusion period, the curve representing blood flow generally returned to the control level in approximately three to four minutes after release of the pressure (Fig. 2). After shorter periods of occlusion, the contour of the initial portion of the graph (and, at times, its height also) remained unchanged, but the descending limb reached the control baseline somewhat sooner (Fig. 1). The range of maximal blood flow response in the different subjects extended over a period of five to twenty seconds after the release of the arterial occlusion pressure.

When the blood flow in the forearm and leg had returned to approximately the same level as the initial resting flow, the readings obtained

thereafter continued to fall within a narrow range on either side of the average control. In the hand, however, in approximately one-half of the cases in which the arterial occlusion pressure was applied for ten minutes or more, the flow, after a brief initial rise, dropped significantly below the control level for a short time, and then approached it again within three or four minutes (Fig. 3). Almost invariably this "negative phase" was associated with a painful feeling in the finger tips which could best be described as a "pins and needles" sensation. The decrease in flow was generally not observed in those subjects who had low control blood flow readings, even though the "pins and needles" sensation occurred. In the patient with a sympathectomized upper extremity (R. M.), the painful sensation was likewise not associated with a negative phase in the hand, although in this case a relatively normal flow was present.

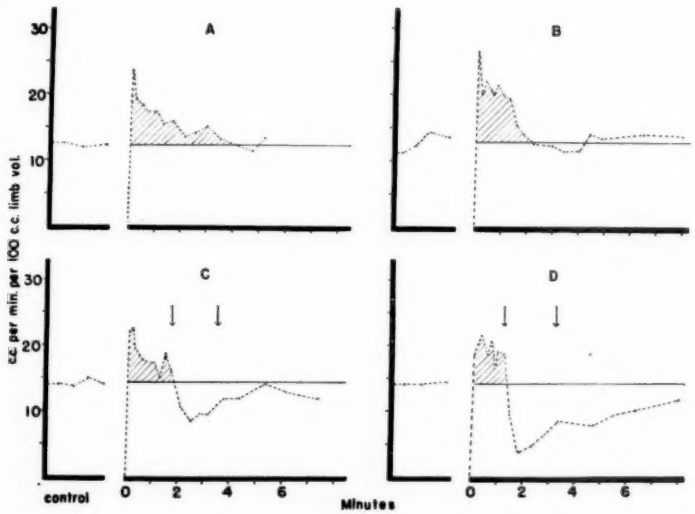

Fig. 3.—Hand. Relationship between negative phase and onset and duration of "pins and needles sensation" in fingers (indicated by period between arrows). Subject L. S. *A* and *B*—five and eight minutes of arterial occlusion (cuff on forearm)—no negative phase and no painful sensation. *C* and *D*—ten minutes of arterial occlusion to forearm and arm, respectively—definite negative phase and severe "pins and needles sensation" (more marked in *D*). Bath temp.—32° C.

It was deemed necessary at the outset to ascertain whether the decrease in flow in the hand was part of the phenomenon of reactive hyperemia, or whether it was merely a nonspecific response of the vessels of the hand to a noxious stimulus. In this connection it was noted that in those cases in which no "pins and needles" sensation was experienced (generally because the occlusion pressure was applied for a period of three or five minutes, instead of ten), there was usually an absence of the "negative phase" (Fig. 3 *A* and *B*). The reverse, as has already been stated, was also true; the painful stimulus was associated with a negative phase (Fig. 3 *C* and *D*) unless the control flow

was low (the only exception to this was the response in the sympathectomized hand). In those experiments in which blood flow determinations were made simultaneously on two hands, with production of reactive hyperemia in only one, a decrease in the resting blood flow in the control hand was observed at approximately the same time that the "pins and needles" sensation and the "negative phase" appeared in the other hand. Further, when both hands were subjected to arterial occlusion, the "negative phase" was always more marked in each than when the arteries to only one were occluded. In addition, the pain experienced by the subject as a result of "pins and needles" sensation in the fingers of both hands was more intense.

At this point it is necessary to emphasize the fact that the forearm and leg rarely, if at all, showed a "negative phase" during the period of reactive hyperemia (Fig. 1). Such dissimilar behavior of the hand, as compared with the forearm and leg, is in accord with the observations of previous workers on the responses of the blood vessels in these sites to noxious stimuli.[4] The above results, together with the fact that a "negative phase" was not observed in the sympathectomized hand, would support the view that this decrease in flow which is frequently present in the normally innervated hand during a period of reactive hyperemia is caused by increased sympathetic tonus resulting from the associated painful sensation. Accordingly, curves from the hand in which there was a "negative phase" have not been included in the results.

Reactive hyperemia at different bath temperatures.—Since at a bath temperature of 32° C. (which is approximately equivalent to normal skin temperature) and at a room temperature of 25° C. there is neither excessive constriction nor excessive dilatation of either skin or muscle vessels, it was possible to study reactive hyperemia in a physiologic state. Examination of Table I reveals that under these conditions the actual blood flow repayment which was elicited by a minute of arterial occlusion was greatest in the hand, somewhat less in the forearm, and least in the leg. It is of interest that the repayment in the different portions of the sympathectomized extremity was grossly similar to that in the normally innervated limb (Table I).

With the extremity exposed to a high bath temperature (43° C.), reactive hyperemia could be studied during a period in which maximal dilatation of cutaneous vessels had already taken place; the muscle vessels were probably not significantly affected by such a procedure. It would follow, therefore, that during reactive hyperemia at the high bath temperature the increased flow is due principally to dilatation of blood vessels in the muscle.

Most of these experiments were performed upon the forearm; the severe pain experienced during the period of occlusion at the high bath temperature made it impractical to utilize the hand, in view of

TABLE I

EFFECT OF DIFFERENT BATH TEMPERATURES ON REACTIVE HYPEREMIA

FOREARM			LEG			HAND		
SUBJECT	CONTROL FLOW	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION	SUBJECT	CONTROL FLOW	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION	SUBJECT	CONTROL FLOW	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION
BATH TEMPERATURE—10° TO 14° C.								
E. F.	0.9	0.6	K. K.	1.2	0.5	J. K.	4.7	0.5
L. S.	0.7	0.5	J. K.	1.5	0.7	J. A.	0.3	0.1
M. K.	0.5	0.4	J. A.	0.4	0.2	C. S.	0.3	0.6
D. A.	1.0	0.9	E. A.	1.4	0.3	K. K.	2.2	0.5
L. B.	0.5	0.4	M. T.	1.4	0.8	D. A.	1.4	0.5
						S. F.	4.2	0.4
						L. S.	4.6	0.2
Av.	0.7	0.5	Av.	1.2	0.5	Av.	2.5	0.4

BATH TEMPERATURE—32° C.

R. J.	1.7	1.5	A. H.	1.1	1.0	E. M.	8.0	3.5
K. K.	1.9	2.3	B. P.	0.9	0.9	P. M.	6.1	2.1
E. M.	2.7	1.3	R. W.	1.0	1.0	E. G.	5.3	3.9
E. G.	0.8	1.5	K. K.	1.5	1.6	D. A.	6.0	2.1
P. M.	2.4	1.5	D. A.	1.4	0.5	P. D.	3.1	1.2
D. G.	1.6	2.0	H. F.	2.6	0.9	D. G.	5.1	1.9
M. M.	1.1	1.1	L. S.	1.1	0.5	M. M.	6.7	1.0
N. R.	1.5	1.7	W. A.	1.7	1.1	J. R.	10.1	1.3
H. S.	0.9	1.6	E. A.	1.7	0.5	L. S.	10.5	1.5
J. R.	2.1	1.6	S. S.	1.5	0.6	C. T.	2.5	2.2
E. L.	1.6	1.1	J. L.	1.1	0.5	F. B.	7.9	1.5
D. A.	1.6	1.3	T. M.	1.4	0.6	L. B.	6.0	2.7
L. P.	1.1	1.8	J. Z.	1.2	0.8	M. A.	3.5	1.4
M. K.	1.0	1.4	D. A.	1.5	0.6	J. Z.	5.9	1.2
L. S.	1.6	1.1	M. L.	1.5	1.0	J. S.	0.8	2.4
C. P.	1.2	1.2	S. F.	0.8	0.3	C. W.	9.6	2.0
C. T.	2.0	1.9	C. B.	0.9	0.8	H. P.	1.7	1.8
C. D.	1.8	1.4	S. L.	1.0	0.5	R. M.	6.8	1.3*
A. F.	2.0	1.3	S. J.	2.2	0.7			
F. B.	1.1	1.2	R. M.	2.2	0.9*			
M. A.	1.7	1.6						
O. H.	1.0	1.0						
R. M.	2.1	0.9*						
Av.	1.5	1.5	Av.	1.4	0.8	Av.	5.8	2.0

BATH TEMPERATURE—43° C.

P. M.	9.3	2.0
R. J.	6.0	1.2
M. S.	10.5	2.2
J. R.	7.8	1.3
D. A.	5.1	2.1
C. T.	8.7	0.8
Av.	7.9	1.6

All control flow readings in c.c. per min. per 100 c.c. limb vol.
*Sympathectomized extremities.

the known effect of noxious stimuli upon the blood vessels of the hand.[2-4] Examination of Table I reveals that the blood flow repayment per minute of arterial occlusion in the forearm was approximately the same at the high bath temperature as at a temperature of 32° C. In the few instances in which the leg was subjected to the same procedure (results not included in the table), the results were similar to those in the forearm.

At the low bath temperature (10° to 14° C.), an opportunity was afforded to study reactive hyperemia during a period in which the blood flow through the cutaneous blood vessels was markedly diminished as a result of the constricting effect of cold. Since the cold does not penetrate to any significant extent below the skin layer,[12] it may be assumed that the resting blood flow figures obtained for the forearm and leg at the low bath temperature represented muscle blood flow primarily. In the case of the hand, however, the possibility existed that in some instances not all of the arteriovenous shunts were entirely closed by the stimulus, with the result that the control flow still included some flow through these vessels. In fact, in some subjects, even when the bath temperature was lowered to 8° or 10° C., the hand flow still remained somewhat elevated. In respect to reactive hyperemia, however, the blood flow repayment elicited by a one-minute period of arterial occlusion in these latter cases was approximately the same as in those in which the control flow was low. Further, the average repayment for the hand, forearm, and leg was also grossly similar. It is of interest that, for at least the hand and forearm, this figure was significantly less at the low bath temperature than that obtained by the same procedure at 32° C. (Table I).

Comparison between the maximal blood flow in response to arterial occlusion and that elicited by direct heat.—In forty-two experiments the resting blood flow of the limb at a bath temperature of 43° C. was compared with the maximal blood flow after a ten-minute period of arterial occlusion at a bath temperature of 32° C. In the hand, the average control blood flow at a bath temperature of 43° C. was 28.2 c.c. per min. per 100 c.c. of limb volume, whereas the greatest flow recorded during a period of reactive hyperemia, at a bath temperature of 32° C., averaged 19.3 c.c. In the forearm the reverse was true; the average control blood flow at the high bath temperature was 7.9 c.c., whereas arterial occlusion at a bath temperature of 32° C. elicited a maximal response which averaged 12.7 c.c. Likewise in the leg, the latter relationship was present; the average control flow at 43° C. was 3.3 c.c., and the greatest flow during reactive hyperemia at 32° C. averaged 7.2 c.c.

DISCUSSION

It is generally held that in normal subjects the magnitude of the hyperemic response which follows deprivation of blood flow is related

to the metabolic needs of the tissues involved. The observations here reported are consistent with such a view when the known facts concerning the regulation of blood flow to the various regions studied are considered. For example, as previously stated, the blood vessels of the hand, in addition to supplying the metabolic needs of the tissues, also function to dissipate heat[1] and possibly to regulate circulating blood volume.[13] Since the function of heat dissipation is active in the hand at ordinary local and environmental temperatures, it would be expected that the control resting flow would be much greater than the amount necessary for metabolic purposes. This is substantiated by our observations, for the blood flow repayment per minute of arterial occlusion at a bath temperature of 32° C. was much less than the theoretical "debt" incurred (equal to control flow per minute). Actually, if the cases in which a negative phase occurred had been included in the series, the average repayment in the hand would have been even less. At extremely low bath temperatures, the resting flow in the hand was in some instances of the same order of magnitude as that in the forearm and leg, and, during reactive hyperemia, the repayment approximately equalled the control flow per minute and, hence, the blood flow "debt" (Table I). In these cases it would appear that the hand was no longer serving the function of heat dissipation, and that its blood flow was dependent chiefly upon metabolic needs.

In the forearm, at bath temperatures of 14° and 32° C., the control flow was quite constant in the same and in different subjects, and the magnitude of the repayment per minute of arterial occlusion approached that of the blood flow "debt" (Table I). Previous studies have demonstrated that, at such local and environmental temperatures, the arterioles in this region are not influenced by sympathetic tonus and are not concerned directly in the process of heat dissipation.[4, 13] The fact that the repayment and the blood flow "debt" were equivalent would suggest that, under these circumstances, the resting flow was dependent chiefly upon the metabolic needs of the tissues. At a bath temperature of 43° C., however, the relation of the resting flow in the forearm to the amount repaid was entirely different; it resembled more closely the response in the hand at 32° C., in that only a small percentage of the "debt" was repaid (Table I). A similar type of response in the forearm has also been obtained by producing extreme degrees of reflex vasodilatation through the application of heat to distant portions of the body.[13] Under these circumstances the forearm was serving the function of heat dissipation, even at a bath temperature of 32° C., and, as would be anticipated, arterial occlusion resulted in a repayment of only a small percentage of the theoretical blood flow "debt." Further evidence was obtained by comparing the resting flows in the forearm at 14,° 32,° and 43° C. (Table I). Those obtained at 43° C. were considerably higher than would be expected as a result purely of increased

TABLE II

EFFECT OF VARYING PERIODS OF OCCLUSION—BATH TEMPERATURE, 32° C.

FOREARM				LEG				HAND			
SUBJECT	CONTROL FLOW	PERIOD OF OCCLUSION MIN.	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION C.C.	SUBJECT	CONTROL FLOW	PERIOD OF OCCLUSION MIN.	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION C.C.	SUBJECT	CONTROL FLOW	PERIOD OF OCCLUSION MIN.	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION C.C.
C. T.	1.7	3	1.8	S. L.	1.1	5	0.4	L. S.	14.2	3	2.6
	2.3	5	1.9		0.9	8	0.5		12.9	5	1.6
F. B.	1.1	3	0.8		0.9	10	0.5		12.8	8	1.6
	1.1	5	1.6	K. K.	1.6	3	0.8	S. L.	10.7	3	3.5
M. A.	1.6	3	1.8		1.2	5	1.1		12.3	5	3.4
	2.1	5	1.3		1.4	10	0.9	C. B.	6.1	5	1.6
	1.5	8	1.7	L. S.	1.1	3	0.5		5.1	8	1.8
C. P.	1.4	5	1.2		1.0	5	0.7		4.5	12	1.4
	1.1	10	1.3		1.2	8	0.5	S. S.	5.8	3	2.1
L. S.	1.4	3	0.9	E. A.	1.7	5	0.8		5.7	5	1.1
	1.7	5	0.8		1.7	8	0.6		5.1	8	1.1
	1.7	8	0.9	T. M.	1.1	3	0.6	C. T.	2.3	3	2.2
	1.9	10	0.9		1.1	5	0.6		2.6	5	2.1
	2.3	12	0.9		1.1	7	0.4	L. B.	7.9	3	1.7
R. J.	1.6	5	1.6	J. Z.	1.2	3	1.0		7.9	5	1.3
	1.9	8	1.2		1.2	5	0.8	M. A.	3.8	3	1.2
	1.6	10	1.7	R. M.	2.3	5	0.9		3.6	5	1.8
S. S.	1.1	3	1.2		2.2	8	1.0		3.0	8	1.1
	1.2	5	1.0	C. B.	1.1	3	0.5	J. Z.	6.6	3	1.2
	1.2	8	1.0		0.8	5	0.8		5.5	5	1.3
R. M.*	2.3	5	0.9		0.9	8	0.8	R. M.*	5.8	5	1.5
	2.0	8	0.9		0.9	12	0.9		4.9	8	1.3
				S. J.	2.5	3	0.8				
					2.0	5	0.7				

Control flow in c.c. per min. per 100 c.c. limb vol.
*Sympathectomized extremities.

metabolism caused by heat. It would then appear that, at high bath temperatures, the total blood flow to the forearm is dependent on factors other than local metabolic needs, whereas, at the lower bath temperatures, a definite correlation exists between the resting blood flow and the metabolic requirements of the tissues.

Further evidence for the view that the blood flow repayment is related to the metabolism of the tissue was obtained by varying the duration of arterial occlusion. In the forearm and leg, and, under certain conditions, in the hand, the magnitude of the repayment was found to be directly proportional to the blood flow "debt" which was incurred (Table II, Fig. 1). This relationship existed for all three bath temperatures. Of course, it must be borne in mind that a blood flow "debt" may be repaid not only by a more rapid rate of blood flow, but also by a greater removal of metabolic products from each 100 c.c. of blood during its passage through the tissues. As a result, a direct relationship between the magnitude of the blood flow "debt" which is incurred and the subsequent increase in blood flow might not always be realized. This may explain some of the results which appear at variance with the majority of the observations (Table II).

It has been found that the magnitude of the first few blood flow levels after release of arterial occlusion is quite independent of the total repayment. This lack of correlation is evident not only in comparing the observations on different subjects, but also on the same subject, after varying periods of arterial occlusion. In some instances the maximal height of the initial blood flow readings after five minutes of occlusion was approximately the same as that after eight or ten minutes; the total number of cubic centimeters of excess blood flow was, of course, smaller for the shorter period (Fig. 1). Such evidence would suggest that the use of the maximum blood flow response during reactive hyperemia as a comparative index of the total response is not justified. Since variations in the shape of the blood flow curve during reactive hyperemia are such that, from a given point in the graph, neither the height of the maximum response nor the amount of the total response can be predicted (Figs. 1 and 2), the procedure of obtaining a single reading at an arbitrarily fixed time after the release of the arterial occlusion pressure[10] is also open to criticism. On the other hand, by obtaining frequent blood flow readings, particularly during the initial portion of the period of reactive hyperemia, one is able to ascertain the maximal blood flow response to a given stimulus, and thus obtain an index of the degree of arteriolar dilatation. In this respect the use of the term "actual blood flow repayment per minute of arterial occlusion" apparently has more significance than "percentage of blood flow debt repaid." This is clearly demonstrated in Fig. 2, in which the repayment for a ten-minute period of occlusion in the hand is recorded in the case of three subjects with varying control blood flow levels. Although the actual repayment

was approximately the same in all three cases, the percentage repayment varied markedly because of the differences in theoretical blood flow "debt"; the latter was derived from the control resting blood flow. Further, in the case of the forearm and leg, because of the relatively low control blood flow readings, very slight variations in response in the different subjects, within the range of experimental error, might make relatively great differences in the percentage repayment.

SUMMARY AND CONCLUSIONS

The effect of arterial occlusion upon the subsequent rate of blood flow was studied in the hand, forearm, and leg in a series of forty-three normal subjects by means of the plethysmographic method.

Evidence is presented to show that estimation of the blood flow repayment after a minute of arterial occlusion is of much greater value than obtaining a figure which represents the single maximum response to arterial occlusion ("per cent of blood flow debt repaid").

It has been found that grossly there is a direct relationship between the duration of the circulatory arrest and the number of cubic centimeters of excess blood flow over and above the control blood flow level.

The direct application of heat has a more potent vasodilating effect upon skin vessels in the hand than the stimulus elicited by a period of arterial occlusion.

The occurrence of a negative phase (reduction of blood flow to less than the control level) in the hand during the period of reactive hyperemia is probably due to the effect of noxious stimuli upon the tonus of the sympathetic nervous system.

These quantitative studies of reactive hyperemia bear out previous observations that the vascular responses of the forearm and leg differ from those in the hand.

If the excess blood flow during reactive hyperemia is considered as a repayment of the blood flow "debt" which is incurred during the period of arterial occlusion, certain conclusions can be drawn concerning the resting blood flow to the various regions which we studied.

Under optimal environmental conditions and at a bath temperature in the range of 14° to 32° C., the blood flow in the forearm and, to a lesser extent, in the leg appears to be regulated chiefly by the metabolic needs of the tissues; at higher bath temperatures, i.e., around 43° C., it exceeds this level. In the hand the resting blood flow is generally greater than that necessary for metabolic requirements, except at extremely low bath temperatures, when the function of heat dissipation is no longer operative.

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THE BLOOD PICTURE IN RHEUMATIC FEVER

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BECAUSE of the absence of a specific diagnostic test for rheumatic fever, we undertook a detailed study of children with acute rheumatic fever. We hoped thereby to shed new light on this malady, which is so obvious in its acute manifestations, so elusive in its subacute state, and so charged with uncertainty when it is quiescent.

In this paper* we shall present several observations on the hematologic picture of 100 hospital patients who were suffering from the disease. Although the blood picture of acutely ill rheumatic patients shows definite, nonspecific changes, they would be of little value in a new, clinically undiagnosed case of rheumatic fever, i.e., one not characterized by pharyngitis or tonsillitis, carditis, fever, or joint or muscle pains. But these nonspecific changes are of value in the prognosis of clinically established, acute rheumatic fever, and of even greater value in estimating the rise and fall of rheumatic activity in a patient who is known to have had the disease. If frequently and accurately repeated, the blood studies on a rheumatic child give a correct index of his status.

Table I summarizes our laboratory work:

TABLE I

NUMBER OF PATIENTS STUDIED, 100; GIRLS, 53; BOYS, 47; AVERAGE AGE, 10½ YEARS

1. Erythrocyte sedimentation rate estimations	1351 during 32 months
2. Nonfilament neutrophil counts	1195 during 32 months
3. Hemoglobin estimations	1164 during 32 months
4. Blood platelet counts	824 during 20 months
5. Coagulation time estimations	721 during 16 months
6. Bleeding time estimations	595 during 15 months
7. Capillary resistance estimations	639 during 22 months
Total	7487

The Erythrocyte Sedimentation Rate is the test most widely used in the diagnosis of rheumatic infection. The following are the observations of some authorities on the significance of this test. Weiss[1] followed the E. S. R. curves in fifty cases of acute rheumatic fever. The rate returned to normal three to seven weeks after the disappearance of complaints. Severity of joint manifestations was not accompanied

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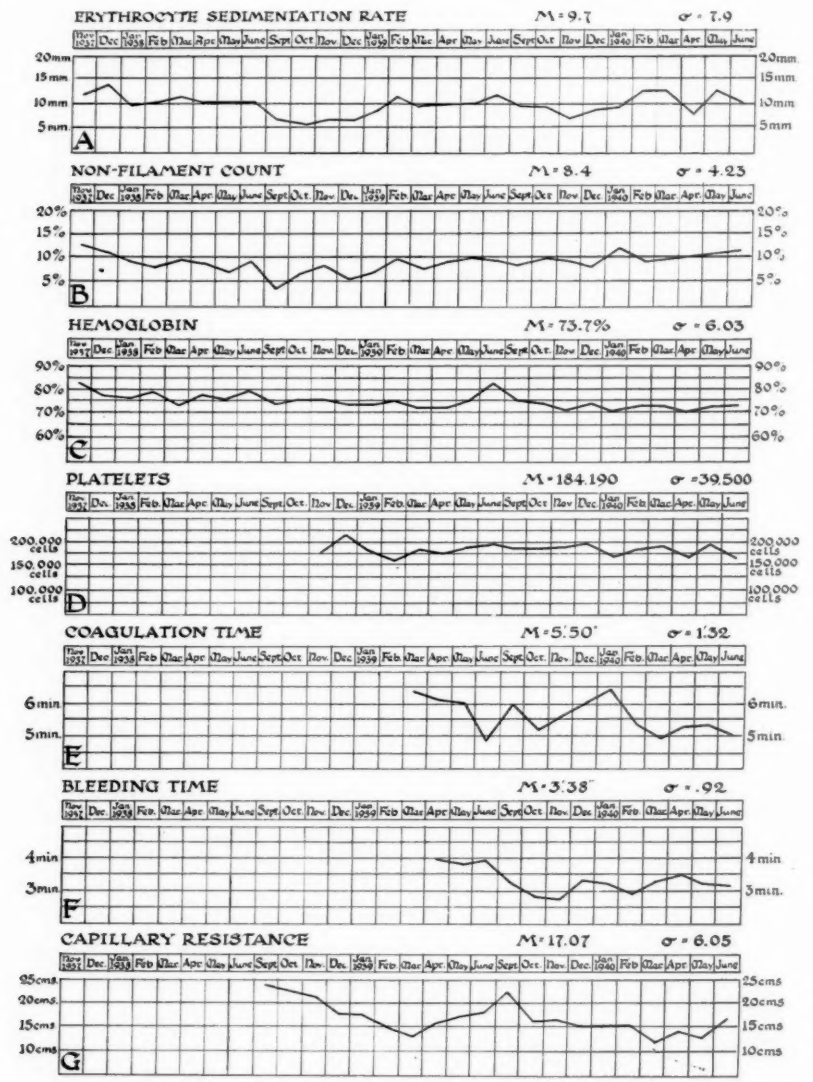
by a proportionately higher E. S. R. Patients with acute rheumatic fever should not be discharged until the sedimentation rate is normal. Payne[2] found that there was a close relationship between the clinical manifestations and the E. S. R.; the latter was of most practical value in following the progress of the patients. Failure to return to normal indicated that some pathologic process still persisted. Bach and Hill[3] observed that the test was of importance as an aid in the initial differentiation between active and nonactive juvenile rheumatism. It was also important if done at regular intervals during convalescence. Hill's[4] opinion was that, if the E. S. R. was normal, active rheumatism, other than chorea, was not present. Struthers and Bacal[5] studied thirty-one patients with rheumatic infection who had 573 E. S. R. estimations and 298 leucocyte counts. They observed that the E. S. R. required months to return to normal, and was the most delicate test for activity of the rheumatic infection. In the presence of cardiac failure with edema, it fell rapidly to levels below normal, and was of serious prognostic significance. Landau[6] discussed the microsedimentation (Linzenmeier-Raunert) method and said that the chief importance of repeated estimations was in indicating the intensity of the acute rheumatic process. The sedimentation rate had to be normal before one could say that the infection had run its course. In uncomplicated chorea the values were low. Elghammer[7] used the Raunert method on 171 patients who were convalescing from various types of rheumatic infections. He found that the E. S. R. served as an indication of rheumatic activity when there were no symptoms. It was valuable in estimating general progress and prognosis. Persistence of a high E. S. R. signified a grave prognosis. Clifton[8] came to the following conclusions: Chorea is the only rheumatic manifestation characterized by a normal sedimentation rate. Active rheumatic infection produces a rapid E. S. R. when arthritis or carditis occurs either alone or as a complication of chorea. Monocyclic rheumatic infection subsides in about two months, as indicated by the sedimentation rate. Coburn and Kapp[9] said that the E. S. R. might be considered a measure of the extent of inflammation. Struthers and Bacal,[10] in their study of 100 cases of rheumatic fever, concluded that the sedimentation rate was the most valuable means of measuring the activity of the rheumatic disease in childhood. Massell and Jones[11] studied 178 patients with active rheumatic fever and found that both the corrected E. S. R. and the leucocyte count were valuable aids in following the course of rheumatic infection, but that the E. S. R. was more useful as a single, isolated test, because the leucocyte count was valueless unless done repeatedly. Massell,[12] in a later publication, said that the E. S. R. was a nonspecific reaction, did not differentiate one disease from another, and had no diagnostic value. He stated that its chief usefulness lay in its ability to detect the presence of a disease process in the absence of all other signs. Struthers[13] contended that

the E. S. R. was probably the most delicate indication of rheumatic activity, and that it was the last abnormality to disappear after activity had ceased.



Graph I.—Mean seasonal distribution of blood findings on 100 rheumatic fever children.

In our studies we used the Linzenmeier-Raunert method of microsedimentation described by Landau.[6] When the same technician did all the tests, we found it simple and accurate for outpatient work. The micromethod has been found equally useful by Elghammer[7] and Rogatz.[14] The latter used the Smith micrometric apparatus. He states that the micromethod which requires the minimal amount of capillary blood

(obtained by a finger prick) is satisfactory and reliable. In our opinion the Linzenmeier method is accurate only up to 50 mm. per hour of sedimentation, after which it becomes difficult to estimate the rate because of packing of the short tube with erythrocytes. The high normal value is taken as 10 mm. per hour. We have also found that the E. S. R. rises during the premenstrual period, and therefore, unless an inquiry is made concerning the menstrual cycle, and other blood findings are taken into account, a serious mistake may occur.

Graph I *A* represents the distribution of the mean E. S. R. estimations in 100 cases of rheumatic fever, active and inactive, over thirty-two months. It will be observed that the highest peaks in the graph correspond to the seasons of greatest rheumatic fever activity, which are reached in November and March, and that there was a slight fall in January and February, and a marked fall from June to September. The mean E. S. R. for the group was 9.7 mm. per hour.

Among the 100 patients who were studied for thirty-two months, fifty-five attacks of rheumatic fever occurred. Twenty-nine patients had thirty-five of these attacks under our observation, either in the wards or in their homes. Of the remaining twenty attacks, some were reported only after the children had stayed for a prolonged period at home in the care of private physicians, and others were seen at the clinic only at the outset of the illness, whereupon the patients were hospitalized in other institutions. In these twenty instances only the record during quiescence was available.

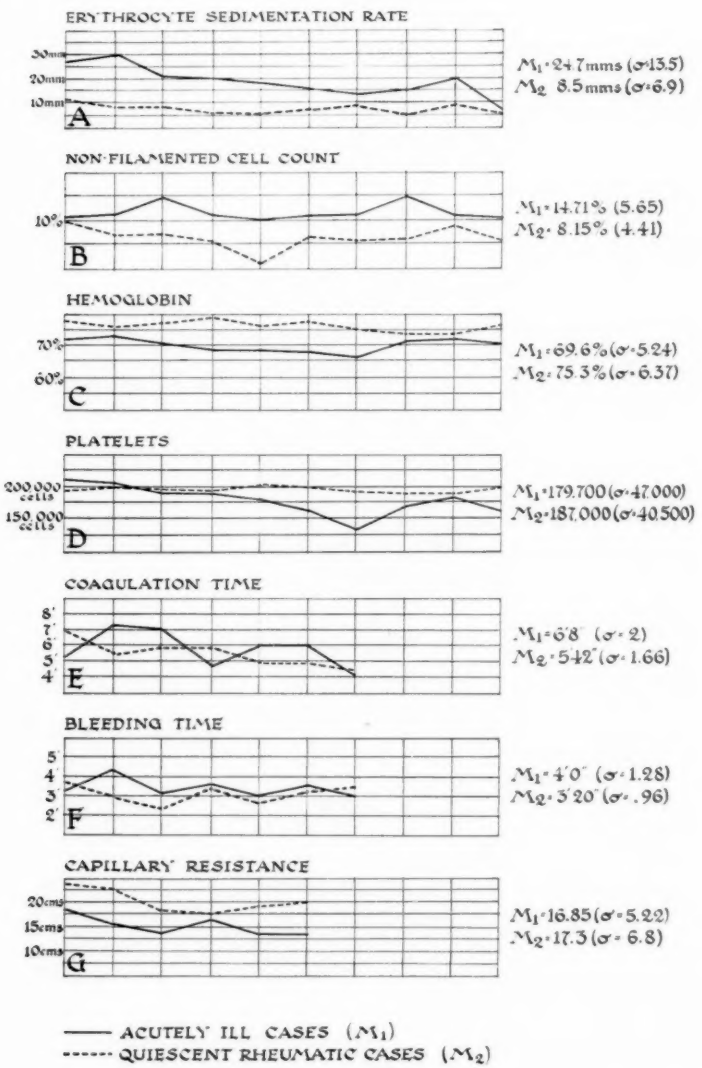
Graph II *A* shows the average trend in the sedimentation rates of the acutely ill and the well rheumatic children. The mean E. S. R. of the acutely ill group was 24.7 mm. per hour, whereas in the well group it was 8.05 mm. per hour. It will be noted that the standard deviation for the first group was abnormally high because of the difficulty of reading values over 50 mm. by the micromethod.

TABLE II

	NO.	MEAN	SIGMA
Total number of patients	100	8.05 mm.	6.9
Boys	47	7.3 mm.	5.7
Girls, all ages	53	8.8 mm.	6.65
Girls menstruating	21	9.9 mm.	6.8
Girls not menstruating	32	7.7 mm.	6.0

To ascertain how much effect menstruation had, we computed separately the E. S. R. of the boys and girls in the quiescent group. The only infections in this group were transient colds which, at times, produced a moderate rise in the E. S. R., and much chronic sinusitis which we found did not accelerate the sedimentation rate. We also calculated the mean sedimentation rate of twenty-one girls who had begun to menstruate and that of thirty-two who had not yet menstruated. The results are presented in Table II.

The above data show that the mean E. S. R. of girls is higher than that of boys, and that that of menstruating girls reaches the upper limit of normal. The E. S. R. of girls who have not yet reached puberty and that of boys is much the same.



Graph II.—Lines representing an average trend in various blood findings in acutely ill and quiescent rheumatic fever patients.

The Nonfilamented Neutrophile Count has only recently become an adjunct to the diagnosis of rheumatic infection, and has not attracted the attention it merits.

The leucocyte count is still regarded by many authorities as an important aid in estimating the intensity of rheumatic infection. We

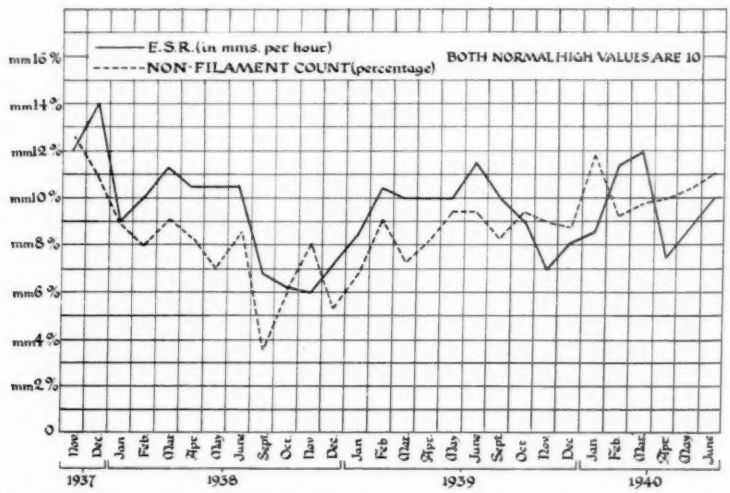
have observed it routinely for four years on all our patients, and have found it unreliable. Even if it is done frequently by the same technician it rarely shows consistent variations, and the personal error is considerable. Therefore, we have abandoned the total leucocyte count in favor of the Schilling count, i.e., the number of nonfilamented neutrophiles in the smear. Little has been published on the Schilling count in the diagnosis of rheumatic fever. Clifton[8] was of the opinion that the Schilling count paralleled the clinical course rather than the subsiding infectious process, and that the E. S. R. was more reliable in the diagnosis of rheumatic activity. Rogatz[15] studied twenty-five cases of rheumatic fever in which both the E. S. R. and the Schilling count were done. He concluded that the E. S. R. was more sensitive as an index of activity and complete convalescence. Both tests were positive when the rheumatic infection was in its early stages, but the Schilling count returned to normal as clinical improvement occurred. Gregg and Allen[16] observed that an increase in the nonfilament count seemed to be more indicative of tissue damage than the polymorphonuclear percentage. Rogatz[17] expressed the view that the Schilling count was of more value than the ordinary differential count in interpreting the clinical manifestations of the acute pathologic conditions of infancy and childhood. King[18] thought that a shift to the left in the number of nonfilamented neutrophiles was not so reliable an index of activity as an increased total leucocyte count. Struthers and Bacal,[19] in their study of 100 cases, observed a marked shift to the left in rheumatic fever. In chorea, with a normal sedimentation rate, there was no association between the Schilling count and the E. S. R.

In our group of 100 patients we made 1193 Schilling counts over a period of thirty-two months; the results are given in Graph I *B*. The average percentage of nonfilamented cells was 8.4. It is readily seen that the number of nonfilamented neutrophiles parallels the sedimentation rate. The parallelism of the curves is particularly striking when they are superimposed. (See Graph III.)

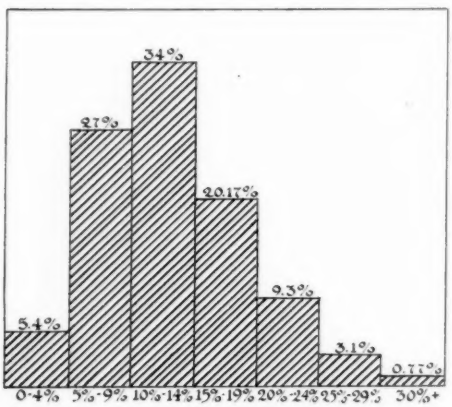
Graph II *B* shows the contrast between the mean nonfilamented cell counts of acutely ill patients and those whose rheumatic infection was quiescent. Again the two curves follow closely the E. S. R. of the ill and well patients, although the nonfilamented neutrophiles were slightly slower to rise at the onset of infection, and returned to normal sooner than the E. S. R.

The distribution of the nonfilamented cells among the ill patients is of interest. Graph IV represents the frequency distribution of nonfilamented cells in the thirty-five cases of acute rheumatic fever that occurred among the 100 patients. It will be seen that 54.17 per cent fell into the category of "moderate shift to the left," i.e., between 10 and 20 per cent, and only 13.17 per cent showed a "marked shift to the left."

The opinion prevails that the E. S. R. is a more sensitive index of infection than the nonfilamented cell count, in that it is usually the first evidence of disease. Let us consider our series of acutely ill patients. Of the thirty-five instances of rheumatic fever under our supervision, in eighteen the E. S. R. and the nonfilament count rose simultaneously, in fifteen the E. S. R. rose before the nonfilamented cell count, and in two the reverse occurred. Thus in more than half of the cases the two abnormalities paralleled each other, and in the remaining seventeen cases the rise of the E. S. R. preceded that of the nonfilamented cells in all but two instances.



Graph III.—Mean seasonal distribution of erythrocyte sedimentation rate and nonfilament neutrophiles in 100 rheumatic fever patients.



Graph IV.—Frequency distribution of nonfilamented neutrophiles in acutely ill group.

Let us now consider the terminal stages of an attack of rheumatic fever and see what happens with respect to the return to normal of the E. S. R. and the nonfilamented cell count. Data are available in

only twenty-nine cases, for in six the attacks had not yet run their course. In seven out of twenty-nine the E. S. R. and the cell count returned to normal at the same time, in fifteen the nonfilamented cell count was the first to become normal, and in seven the E. S. R. was first.

If the E. S. R. is to be regarded only as an index of infection, then our small series of cases suggests that the sedimentation rate is the more sensitive of the two tests, both at the beginning and at the end of an attack of acute rheumatic fever, especially the latter. But we must bear in mind that the E. S. R. rises also before menstruation, which may coincide with the beginning or at the end of a rheumatic attack.

The Hemoglobin content of the blood in rheumatic fever gets scant attention in medical writings. Weiss[1] said that anemia always accompanies rheumatic fever. Geselius[19] observed an association between the degree of anemia and the severity of the rheumatic infection. Hubbard and McKee,[20] in a study of seventeen cases, spoke of a frequently severe anemia with the active phase of rheumatic fever, and commented that its persistence might often be an indication of continued rheumatic activity. Isaacs, Sturgis, Bethell, and Goldhammer[21] believed that the occurrence and severity of anemia were an accurate index of rheumatic activity. They also pointed out that the E. S. R. paralleled the severity of the anemia, and that both should be watched in following the course of the disease.

Over a period of thirty-two months we made 1164 estimations of hemoglobin in our group of 100 rheumatic patients. Using the Sahli method, the hemoglobin was measured in grams, from which the percentage was computed (16.7 grams equal 100 per cent).

Graph I *C* shows the seasonal distribution of the mean hemoglobin curve for the entire group of patients, including those with active and inactive disease. There was a general downward trend from a high peak in November, 1937, toward May, 1938. Then there was an abrupt rise in June to 78.3 per cent. In September the hemoglobin fell to 74 per cent, then maintained a fairly steady level between 75 per cent and 74 per cent until the middle of March, 1939. At that time a fall to 72 per cent occurred, and was maintained until the end of April, when a rapid rise took place, so that by the end of June an average of 82 per cent was attained. In September, 1939, the hemoglobin returned to 75 per cent. During the winter of 1939-40, the hemoglobin was uniformly low, fluctuating between 73.5 per cent and 70 per cent, without the expected rise in May.

In the hope of shedding light on the continuous decline in the mean hemoglobin level of the entire group during three consecutive winters, we present the mean hemoglobin percentage, together with the number of attacks of acute rheumatic fever which were observed during each of the three periods, and the atmospheric temperature for the first six

months of each year, i.e., from January to June, which covers the period of greatest rheumatic activity (Table III).

The steady fall in hemoglobin during the three consecutive winters may have been related to the increasing frequency of rheumatic fever attacks, which, in turn, may have been associated with the steadily diminishing temperature during the three January-to-June semesters. Vital statistics for New York show that the first half of 1938 set a record for low mortality from rheumatic heart disease, and from scarlet fever and pneumonia, as well. It was also the warmest half year of the three, with a temperature of 449° above average. The temperature during the first six months of 1939 was lower. All of the eight attacks of rheumatic fever in our series occurred during that period, and the average hemoglobin dropped 2.3 per cent. The year 1940 was characterized by the coldest and rainiest winter and spring of the three years (precipitation 24.66″), and twelve rheumatic fever attacks out of a total of sixteen occurred between January and June of that year. The hemoglobin was lowest during that winter, and there was no rise in May.

TABLE III

	1937-38	1938-39	1939-40
Mean hemoglobin	77%	74.7%	72.35%
No. of attacks of acute rheumatic fever	11	8	16
No. of attacks between January and June	6	8	12
Mean temperature* from January to June	+449°	+374°	−366°

*These figures represent the cumulative deviation from the mean temperature, as reported by the U. S. Weather Bureau of the first six months of each of the three years.

Graph II *C* shows the different mean hemoglobin levels of the acutely ill patients and those whose disease was quiescent. In the former it was 69.6 per cent, and, in the latter, 75.35 per cent. Hemoglobin values under 59 per cent occurred in only nineteen of 1164 estimations (1.6 per cent).

Obviously, many factors other than infection and atmospheric temperature determine the hemoglobin content, e.g., diet, hygiene, and hereditary and individual make-up. The latter is important, and that is why one cannot put too much reliance on occasional estimations of hemoglobin in the diagnosis of rheumatic fever. We have normal standards for the sedimentation rate and the nonfilamented cell count, but there are, apart from the acute anemias, only individual standards for hemoglobin. A child who shows no evidence of infection and maintains a steady hemoglobin level of 68 per cent is better off than the one whose hemoglobin suddenly drops from 90 per cent to 75 per cent after an attack of acute tonsillitis.

Platelets, Coagulation and Bleeding Time.—During the first year of our study our observations were confined to the estimation of the

erythrocyte sedimentation rate, nonfilament count, and hemoglobin. In the course of our clinical observations we were much impressed by the frequency of hemorrhagic phenomena in rheumatic patients. Forty-three per cent reported more than two nosebleeds, more than two petechiae at a time were observed in nineteen cases, and 11 per cent of the patients had purpuric spots as a result of insignificant trauma. Hoping to shed more light on the nature of these hemorrhagic symptoms, in the fall of 1938 we added a routine platelet count to our study, and, a few months later, when our laboratory facilities expanded, the estimation of coagulation and bleeding time.

This study particularly interested us because there is almost no mention of it in medical writings, although a great deal has been written about the blood-clotting mechanism and the purpuras, and some attention has been given to hemorrhagic manifestations in scarlet fever. We present here the few references that have a direct bearing on this study and on our observations. The most valuable monograph on blood platelets is that of Tocantins.[22] He observed that during the acute stage of infectious diseases, including rheumatic fever, there is a thrombopenia which gives place at the termination of the infection to moderate thrombocytosis. The thrombopenia and the decrease in the number of platelets correspond to the duration of fever. Tocantins is the only writer who refers directly to rheumatic fever. Hunt[23] said that hemorrhages come on usually after the subsidence of the acute symptoms of scarlet fever, and seem to be caused by the action of scarlatinal toxin on the endothelium of the blood vessels. In most cases there were a sharp reduction in the platelets and prolongation of the bleeding time. Coburn[24] said that the frequency of epistaxis, purpura, hematuria, and hemorrhagic pulmonary consolidation during the activity of the rheumatic process strongly suggested that there were physiologic changes causing increased permeability of the capillaries and small blood vessels. Sturgis, Isaacs, Goldhammer, and Bethell,[25] in their review of publications on the hemorrhagic state, noted that bleeding may result from the decrease in blood platelets, alteration in the plasma, or changes in the permeability of the capillaries. Madison and Squier[26] found that increased permeability of the capillary walls to erythrocytes is always a pathologic condition and demands an etiologic investigation. They added that capillary erythropermeability is associated with vitamin C deficiency, severe infections, terminal phases of malignant disease, malignant hypertension, primary blood disease, allergic states, and ovarian disorders. McKhann and Edsall[27] were of the opinion that purpura implies some factor which causes a reduction in blood platelets. The presence of purpuric manifestations in allergic states, as well as in infections, suggested to them an imbalance among the various factors which are involved in the normal coagulation process. Elliott[28] said that in primary or idiopathic thrombocytopenic purpura the plate-

lets are markedly reduced, or may even be absent, bleeding time is prolonged, and clotting time delayed. He also stated that, in almost all cases, purpura is a symptom complex rather than a disease entity. Rosenthal[29] observed that thrombopenic purpura shows uniformity in its blood picture, but presents a marked variation in its course from acute to chronic. He noted a marked diminution in blood platelets, prolongation of the bleeding time, and clot retraction. Fox and Enzer,[30] in a paper on the phenomena of purpura following scarlet fever, expressed the opinion that the reasonable explanation for the purpura was that scarlet fever toxin strongly affects the capillary epithelium.

Before we present our observations on the subject, we shall review what different authorities regard as normal values for the platelet count and coagulation and bleeding time.

Platelets.—Levinson and McFate:[31] normal values are from 250,000 to 350,000 per c. mm. of blood. Tocantins:[22] average platelet count on normal persons is 250,000 ± 7,000 per c. mm. of blood, with a standard deviation of 58,000. Todd and Sanford:[32] the normal number of blood platelets, when counted by the direct method, ranges from 200,000 to 300,000 for each c. mm. of blood.

Coagulation Time.—Levinson and McFate:[31] capillary method, normal time is from three to eight minutes. Pepper and Farley:[33] capillary method, two to four minutes. Nicholson:[34] capillary method, two to eight minutes.

Bleeding Time.—Levinson and McFate:[31] by the Duke method, the normal bleeding time is from three to seven minutes. Todd and Sanford:[32] the normal bleeding time is from one to three minutes, but may be as long as eight minutes. Pepper and Farley:[33] in normal persons a small, sharp cut through the skin bleeds from three to six minutes. The bleeding time is in inverse proportion to the number of platelets. Nicholson:[34] normal bleeding time is from three to five minutes.

In our study we considered that the normal platelet count is between 250,000 and 350,000 per c. mm., that the coagulation time varies from three to five minutes, with a high normal limit of seven minutes, and that the bleeding time ranges from one to three minutes, with an upper limit of five minutes.

The personal error in our series of computations on platelet counts was ± 4,500 cells. The platelets were counted by the direct citrate method; the coagulation time was ascertained by Zabrazes' capillary method, and the bleeding time by the direct capillary method.

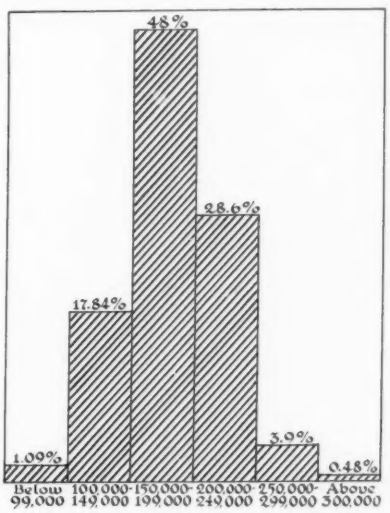
In the course of twenty months we did 824 platelet counts on 100 rheumatic fever patients, and found that only 4.38 per cent had counts above 250,000 cells per c. mm. Graph V shows the frequency distribution of these 824 platelet counts. Nearly one-half were between 150,000 and 200,000, and 66.93 per cent were below 200,000, which is low by all standards. Graph I *D* shows the mean seasonal distribution of platelets through the twenty months of observation. The lowest values occurred in April and May of both years, when the E. S. R. and nonfilamented cell counts were high. The mean platelet count for the whole group was 184,000 per c. mm. There was no appreciable dif-

ference between the counts on boys and girls, nor between menstruating and nonmenstruating girls. The latter observation corroborates Lee and Erickson's[35] work on hemophilia and the blood of menstruating women, in that in both conditions there is no reduction of platelets, but a delay in their disintegration. Table IV summarizes the above data.

The platelet count of the acutely ill children was, on an average, 7,300 cells lower than that of the ones whose disease was quiescent. Graph II *D* shows that after the onset of infection there is at first a moderate decrease in blood platelets, followed by a more rapid diminution, and then a rapid recovery at the end of the attack.

TABLE IV

	NUMBER	MEAN	SIGMA
Total patients	100	184,190 platelets	39,500
Boys	47	183,950 platelets	44,740
Girls	53	185,500 platelets	36,000
Girls menstruating	21	185,000 platelets	27,000
Girls nonmenstruating	32	186,900 platelets	27,500



Graph V.—Frequency distribution of platelets in 100 rheumatic children.

Seven hundred twenty-one coagulation time estimations were done on our 100 patients in the course of sixteen months. Graph I *E* shows the mean seasonal variations of the coagulation time. The values were low in May, 1938, and in March and June, 1939, and elevated during the winter months. The mean coagulation time for the group was 5′50″. This is well within normal limits, although higher than the average for normal persons. Sex played no role in the length of the coagulation time; that of boys was only a fraction higher than that of girls. There was also no difference between menstruating and nonmenstruating girls. Graph II *E* shows that in the group of children who were suffering

from acute rheumatic fever the mean coagulation time was 6′8″, and in the well group it was 5′42″.

Five hundred ninety-five bleeding time estimations were recorded in the course of fifteen months on the 100 children. We found that the mean bleeding time for the entire group was 3′38″, which is also within normal limits. The average bleeding time for the girls was 3′29″, and for the boys eighteen seconds longer. Graph I *F* shows the seasonal variations in the bleeding time of our patients. The longest were recorded in April and June, 1939, and in April, 1940. Graph II *F* shows that the mean bleeding time was four minutes for the acutely ill patients and 3′20″ for the well group. Our observations on the coagulation and bleeding times are summarized in Table V.

TABLE V

	COAG. TIME, MEAN	SIGMA	BLEEDING TIME, MEAN	SIGMA
Total Group	5′50″	1.3	3′38″	0.92
Boys	5′56″	1.67	3′47″	1.1
Girls	5′49″	1.5	3′29″	1.03

From the above data it appears that the platelet count is of value in cases of rheumatic fever, because of the uniformly low counts, and because a marked decrease occurs during the later phase of infection, but, as far as the bleeding and coagulation times are concerned, the slight variations are so well within normal limits that as isolated tests they appear to be of no value.

Capillary Resistance.—We also sought an explanation for rheumatic hemorrhagic phenomena in capillary permeability. A detailed article by us[36] on the subject of capillary resistance in rheumatic fever is being published elsewhere. Therefore, we shall present data which are pertinent only to this report.

Capillary erythropermeability has been attracting considerable attention lately. We have already mentioned the article of Madison and Squier[26] on the subject. Wilder and Wilbur[37] observed that increased capillary fragility is nonspecific, and occurs in a variety of conditions other than vitamin C deficiency. They also showed that patients with scurvy fail to give evidence of increased capillary fragility. Greene,[38] in his discussion of the variation in capillary resistance of the same children at different times, concluded that a positive reaction to the capillary resistance test does not necessarily denote an insufficient intake of vitamin C. Zander,[39] in his article on inflammatory changes in blood vessels, said that bacterial agents, after an increased initial resistance, produce a diminished resistance to capillary permeability. When inflammation is present in a sensitized animal the preliminary period is shortened and the capillary fragility hastened. Rossman[40] observed that artificially induced fever causes an immediate decrease in capillary resistance. Brown[41] noted increased capillary permeability in scarlet fever.

Out of our group of 100 patients, only eighty had capillary resistance studies sufficiently extensive to be included in this article. We used exclusively the simple method described by Dalldorf.[42] We found that the Dalldorf capillary resistometer was an effective means of estimating accurately and repeatedly the capillary erythropermeability. Abt, Farmer, and Epstein[43] reported that the normal capillary resistance of 10-year-old children was 23 cm. of negative pressure. The average age of the patients in our group was 10.5 years. Our average for the group of rheumatic fever patients over a period of twenty-two months of study was 17.07 cm. of negative pressure. The highest mean capillary resistances were recorded in September, 1939 (24 cm.), and in September, 1940 (23 cm.); the lowest were noted in March, 1939 and 1940, when they were 13 and 12 cm., respectively (See Graph I *G*). The latter coincided with the onset of rheumatic activity and remained at a low level until May of both years, when clinical and hematologic improvement occurred.

Forty-six estimations of erythropermeability were made during fourteen attacks of acute rheumatic fever. The mean capillary resistance of ill children was 16.85 cm., and that of well patients averaged 17.3 cm. (See Graph II *G*). The capillary resistance of the boys was 17.3 cm., and, of the girls, 16.7 cm. The greatest capillary permeability was noted in forty-three children who had had repeated nosebleeds. Their capillary resistance was only 16.6 cm., whereas that of those who had had no bleeding was 18.6 cm.

These data are presented in Table VI.

TABLE VI

TOTAL NUMBER OF PATIENTS, 80	BOYS, 39	GIRLS, 41
Average for the Group	17.07 cm.	Sigma 6.05
Average for the Boys	17.30 cm.	Sigma 6.60
Average for the Girls	16.70 cm.	Sigma 6.00
Average for the Bleeders	16.60 cm.	Sigma 5.05
Average for the Nonbleeders	18.60 cm.	Sigma 7.75

COMMENT

Our study corroborates the prevailing opinion that the erythrocyte sedimentation rate is the most delicate nonspecific indication of rheumatic infection. In using it, allowance must be made for the premenstrual period, and also for acute anemias, which we did not encounter in our group of patients. The mean E. S. R. of menstruating girls is higher than that of girls under puberty and of boys.

The E. S. R. is valuable as an isolated test because of its sensitivity to the presence of infection and because of its well-established normal values. In thirty-three of our thirty-five cases of acute rheumatic fever the E. S. R. was abnormal at the outset of the attack; in one case it rose late; and in only one did it never rise, even in the presence of

other hematologic and clinical evidences of infection. Many transient upper respiratory infections in our cases were accompanied by a moderate rise in the E. S. R. but it would fall to normal within a few days. When an upper respiratory infection ushered in an attack of rheumatic fever, the E. S. R. would remain accelerated or would continue to rise after the symptoms of the cold had subsided. A single E. S. R. estimation when the patient is not menstruating indicates merely the presence or absence of an infection, and, even when the child is known to be rheumatic, does not necessarily indicate an exacerbation of the disease, but often just the presence of an intercurrent infection. Only the trend of the E. S. R. curve, together with other clinical and laboratory aids, has diagnostic importance. In cases of acute rheumatic fever, the E. S. R. takes, on an average, two months to return to normal. When the E. S. R. returns to normal in the course of a few days, or even two weeks, it means that the patient has had an infection other than rheumatic fever.

The nonfilamented neutrophile count is an important diagnostic criterion of infection. It is not so sensitive as the E. S. R., but has the advantage that an increase in the nonfilamented cells is always evidence of infection, and often a severe one. With most transitory colds, the Schilling count in our cases remained normal, whereas the E. S. R. was moderately accelerated. We found that a cold which was unaccompanied by an increase in the nonfilamented cells gave us less cause for concern than one accompanied by a count above 10 per cent. During acute attacks of rheumatic fever the nonfilamented cell count closely paralleled the trend of the sedimentation rate, except in the terminal stages, when it returned to normal sooner than the E. S. R. A normal Schilling count does not mean that infection is absent, but it does mean that either the infection is trivial or is just beginning, and that there is, as yet, no effect on the bone marrow.

The hemoglobin level is an unreliable standard of activity, if used as an isolated test. Only the trend of the hemoglobin curve has significance in a given case. In evaluating the intensity of infection with the aid of hemoglobin estimations, the question should always be asked: what is the patient's average hemoglobin level during periods of rheumatic inactivity? The average, not the maximum, should be taken for comparison, because even in health the hemoglobin exhibits marked variations. Very few of the children in our series had a hemoglobin under 59 per cent, but many showed a sudden and significant fall, amounting to 15 per cent, during an acute infection. Hence a single estimation is useless, and only repeated estimations which indicate a downward trend in hemoglobin may be considered significant.

In our effort to account for the hemorrhagic phenomena of rheumatic fever, our attention was first turned to the blood platelets. Of 823 counts on the entire group of patients, 66.93 per cent were below 200,000,

and only 4.38 per cent were above 250,000. We wish to draw special attention to this sharply subnormal platelet count in children who are subject to rheumatic fever; it characterizes the quiescent state as well as the acute. There was no difference between the boys and the girls in this respect. The presence of an acute infection produced a sharp decrease in the platelets only toward the end of the attack, and this was followed by a rapid rise.

The estimation of bleeding and coagulation time shed little light on the bleeding tendency of rheumatic fever patients. Both showed marked seasonal variations which were coincident with peaks of infection, but these variations were so obviously normal that for diagnostic purposes they had no significance. As in the case of hemoglobin, knowledge of the average bleeding and coagulation times for each patient during the quiescent period is of importance in appreciating the variations during disease.

We found that the estimation of capillary resistance was important in the diagnosis of the rheumatic state. The test is easy to perform, normal values are known, and both patients with active and inactive rheumatic disease show considerable deviations from the normal. The lowest capillary resistances were observed in children who had had repeated attacks of epistaxis. The capillary resistance displayed marked seasonal variations; the lowest erythropermeability occurred during the spring months, when the incidence of rheumatic fever attacks was greatest.

It appears that the hemorrhagic tendency of the rheumatic state may be explained by (1) the generally low blood platelet level, with further reduction during the acute phase of the disease, and (2) the increased capillary erythropermeability of all rheumatic fever patients, especially those who are prone to nosebleeds and have acute attacks of fever.

CONCLUSIONS

Seven tests are enumerated below in the order of their diagnostic significance.

1. The erythrocyte sedimentation rate is the most delicate means of detecting the presence of an infection, even a trivial one. In the absence of clinical manifestations, it is an error to assume that rheumatic infection is present when an elevation of the sedimentation rate is the only abnormality. The E. S. R. is accelerated when there is anemia and before menstruation. It is important as a routine test in cases of known rheumatic disease, and is even more valuable in following the course of an acute attack.

2. The nonfilamented neutrophile count is not so delicate a test as the sedimentation rate, but should be used routinely on all patients with rheumatic fever, because an increase in the number of nonfilamented neutrophiles *always* indicates the presence of an infection, often a severe one. As an isolated test it is important.

3. The capillary resistance is next in diagnostic importance, not only because of the generally increased erythropermeability of rheumatic fever patients, but also because of the marked variations in the active and inactive phases of the disease. It is lowest in children who are prone to hemorrhagic phenomena.

4. Sixty-six and ninety-three hundredths per cent of the platelet counts on our patients were below 200,000 per c. mm. There is a progressive reduction of platelets during the initial phases of an acute attack, with a marked fall during the later weeks, followed by a rapid rise.

5. The hemoglobin estimation is not important as an isolated test unless the trend of the hemoglobin curve of the patient is known.

6. and 7. Coagulation and bleeding time estimations offer no aid in the diagnosis of rheumatic fever because their variations are practically always within normal limits, although in acutely ill patients they tend to show high normal values.

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ONE EAST END AVENUE

VENOUS PRESSURE RESPONSES TO EXERCISE

Preliminary Report

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THE main reason why measurement of the venous blood pressure is not adapted to routine clinical use is that the results obtained by the usual technique are not sufficiently reliable to be of great clinical importance. Venous pressure readings on normal persons, as recorded by different authors, show a wide variation. The range of this variation is still greater when different methods are compared. In many cases of heart disease with decreased functional capacity of the cardiovascular system, the venous pressure at rest is within normal limits, and it rises only when there is clinical evidence of congestive heart failure. Certain American authors[1] stated recently that, in their experience, venous pressure measurements have been of little diagnostic aid in borderline cases of congestive heart failure.

For this reason, efforts have been made to devise a method of measuring the venous pressure during and after bodily exercise, in order to obtain a more reliable evaluation of the pathophysiologic events in the cardiovenous system.

Venous pressure responses to exercise have been investigated by Hooker,[2] Schott,[3] Villaret, and others,[4, 5] Bedford and Wright,[6] White, Barker, and Allen,[7] Schneider and Collins,[8] and, recently, by Nieuwenhuizen.[9] All these authors observed a rise of venous pressure with muscular exertion which lasted usually throughout the whole period of the activity. White, Barker, and Allen[7] found in normal subjects that the venous pressure rose a few centimeters of water during exercise. It fell to, or below, the control level immediately on cessation of the exercise. Subjects with congestive heart failure had a high resting venous pressure, which rose considerably on exercise and did not return to normal when it ceased. Nieuwenhuizen[9] followed the venous pressure for ten minutes after exercise, and arrived at the conclusion that in normal subjects the venous pressure falls to its resting level within fifteen seconds after exercise. He observed in cases of slight congestive heart failure that the resting value was normal, and that only the response to exercise betrayed the pathologic condition.

This preliminary report is based upon 122 exercise tests on eighty patients. The group is small, and the purpose of this article is not to

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draw conclusions, but to record our observations. We believe that the results we obtained may be of interest and value for further investigations.

METHOD

We employed the air-filled system, with an aneroid manometer. This method is suitable for clinical use, and even for serial measurements lasting some minutes, when technical precautions are strictly maintained. For details of the technique, reference should be made to the works of Villaret, and others,[10] and Bedford and Wright.[6] After having ascertained the resting value, the subject was told to raise, successively, the right and left leg ten times each, keeping the upper part of the body as still as possible. The venous pressure was taken immediately on cessation of the exercise, and then thirty seconds, and one, two, and three minutes after it ceased. In this way a venous pressure curve consisting of six readings was obtained. In some cases, the communication between manometer and vein was maintained during the whole experiment, even during exercise, and the readings so taken were compared with those obtained on the same subjects when communication had been interrupted, and restored only at the moment of the measurements. No differences were found. The needle, the metal nozzle, and the short piece of rubber tubing were syringed with 3.8 per cent sodium citrate solution just before the experiment, in order to avoid blood coagulation. The blood usually remained fluid until the end of the experiment (four to five minutes); if it did not, which happened very rarely, the results were rejected.

RESULTS

In eight cases, in which there was neither clinical nor electrocardiographic evidence of heart disease, the resting venous pressure was normal (from 6 to 12 cm. of water). It rose about 2 to 5 cm. of water during exercise, and returned to the basal level within thirty seconds after exercise was stopped (see Fig. 1). These observations are in agreement with those of White, Barker, and Allen,[7] and Nieuwenhuizen.[9]

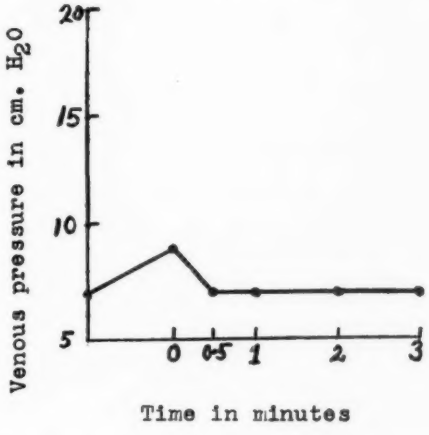

Fig. 1.—Normal venous pressure response to exercise.

In thirty-eight out of fifty-four cases (70.3 per cent) in which there was clinical evidence of congestive heart failure, the resting venous

pressure was increased (above 12 cm. of water), and the response to exercise was a pathologic one, irrespective of the nature of the cardiac disease. The venous pressure showed a greater rise during exercise, and it either returned to the initial level more slowly than in normal subjects, or not at all during the period of observation. In twelve of the sixteen cases of this group in which the resting values were normal, the venous pressure curve after exercise was pathologic in the sense mentioned above, which was in keeping with the clinical evidence of venous engorgement. In four cases, both the resting value and that after exercise were within normal limits.

Of eighteen patients with heart disease without any clinical evidence of congestive heart failure and with a normal venous pressure at rest, eight exhibited a normal response to exercise. In the remaining ten cases, the venous pressure rose considerably during exercise and fell below the initial level after it. This fall of the venous pressure after exercise has been noted by Nieuwenhuizen,[9] who explained it as a regulative mechanism. He stated that this kind of response may indicate latent congestive heart failure.

In our experience, auricular fibrillation, per se, does not alter the venous pressure. In our cases of auricular fibrillation, the venous pressure was increased only when the fibrillation was associated with congestive heart failure. However, in cases of auricular flutter the venous pressure seemed to be rather subject to pathologic alterations. It is difficult to explain this observation. The question whether the mechanism of auricular flutter, per se, is able to alter one or more factors which are responsible for the maintenance of normal peripheral venous pressure requires further investigation.

ILLUSTRATIVE CASES

CASE 1.—L. P. was a man, aged 60, who had heart sounds of poor quality and a presystolic gallop rhythm. His blood pressure was 190/100. There was no evidence of venous engorgement. Roentgenologically, the left ventricle was enlarged. The electrocardiogram showed complete A-V heart block. The blood Wassermann reaction was negative. The venous pressure was normal at rest, and fell below the initial level after exercise (Fig. 2). Diagnoses: complete heart block, probably caused by coronary sclerosis; no clinical signs of congestive heart failure; venous pressure normal at rest, with a pathologic response to exercise which may have indicated a decrease in the functional capacity of the cardiovenous system.

CASE 2.—M. S. was a woman, 40 years of age, who had the auscultatory signs of mitral stenosis and aortic incompetence. Her pulse was irregular. The blood pressure measured 110/50. There was venous engorgement in the neck, râles were heard over the basal portions of the lungs, the liver was slightly enlarged, and there was slight edema of the lower extremities. Roentgenologic examination showed that the heart was symmetrically enlarged. The electrocardiogram revealed auricular fibrillation and low voltage of the QRS complexes. The venous pressure at rest was slightly above normal; it showed a pronounced rise during exercise, and did not return to the initial level until three minutes after exercise (Fig. 3). Diagnoses: rheumatic

mitral stenosis and aortic incompetence, with clinical signs of congestive heart failure. The venous pressure readings and clinical manifestations were in agreement.

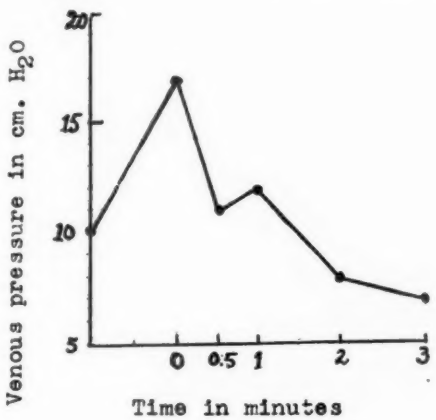

Fig. 2.

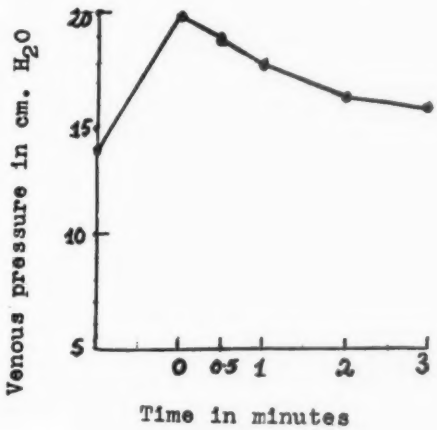

Fig. 3.

Fig. 2.—Normal venous pressure at rest. Pathologic response to exercise; pronounced rise and fall below the initial level.

Fig. 3.—Slightly increased venous pressure at rest. No return to the initial level until three minutes. Evident pathologic response to exercise.

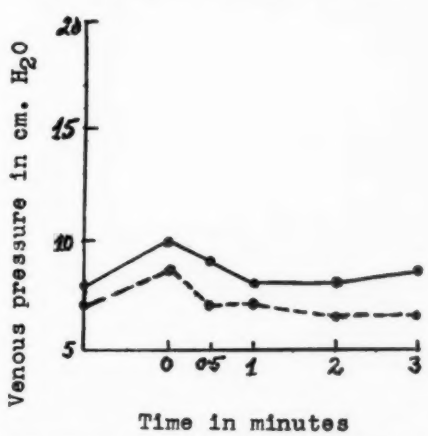

Fig. 4.—Normal venous pressure curve both during fibrillation (solid line) and sinus rhythm (dotted line).

CASE 3.—J. E. was a 39-year-old man who had auricular fibrillation without any evidence of a valvular lesion. There were no signs of congestive heart failure. The blood pressure was 120/80. Roentgenologically, the heart was normal in size and shape. The electrocardiogram showed auricular fibrillation, with normal ventricular complexes. The administration of quinidine abolished the auricular fibrillation. The venous pressure curve was normal both when he had fibrillation and after normal sinus rhythm had been restored (Fig. 4). Diagnoses: auricular fibrillation of uncertain etiology; no clinical evidence of congestive heart failure; normal venous pressure.

CASE 4.—J. G., a 45-year-old man, had auricular flutter and no clinical manifestations of congestive heart failure. The blood pressure was 115/80. Roentgeno-

logically, the heart was normal. An electrocardiogram which was made after cessation of the auricular flutter showed sinus rhythm, with T-wave inversion in the standard leads. The details of the venous pressure measurements are shown in Fig. 5. Diagnosis: paroxysmal auricular flutter, probably caused by coronary artery disease. The venous pressure was abnormally high at rest when flutter was present, and showed a pathologic response to exercise; after sinus rhythm became re-established the resting value was normal, and the response to exercise was nearly normal.

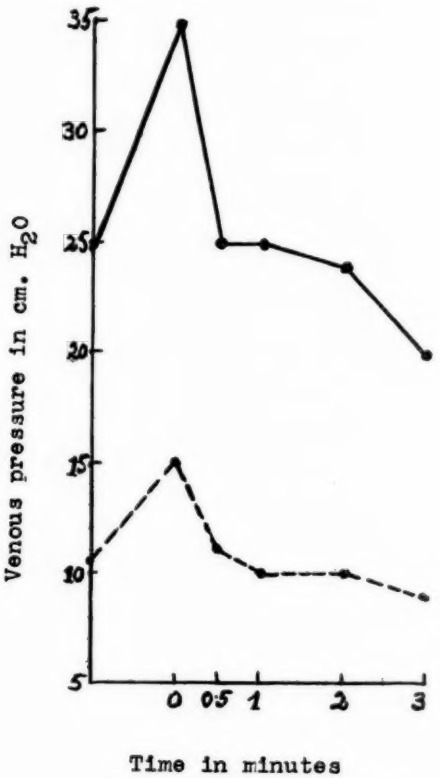

Fig. 5.—Pathologic venous pressure curve during auricular flutter (solid line). Nearly normal venous pressure curve during sinus rhythm (dotted line).

DISCUSSION

It is well known that exercise is accompanied by an elevation of the venous pressure. It may be emphasized that the degree of this elevation and the time necessary for the venous pressure to return to its basal level after exercise seem to be important factors in evaluating the functional capacity of the cardiovenous system.

In our normal subjects there was only a slight rise in venous pressure during exercise (about 1 to 4 cm. of water), and it reached its initial level within thirty seconds after exercise and never fell below it.

In some cases of heart disease without any clinical signs of congestive heart failure, the resting value was within normal limits, but in

the exercise experiment, after a rise of several centimeters of water, the venous pressure dropped below the initial level. White, Barker, and Allen[7] and Nieuwenhuizen[9] found that there was a slight fall below the basal level after exercise, not exceeding 1.5 cm. of water (Nieuwenhuizen), even in healthy young people. A greater fall below the original level was considered by Nieuwenhuizen as a pathologic reaction, and our observations support this view. It is open to question whether the fall of venous pressure below the initial level after exercise is due more to retrograde influences from the heart than to temporary changes in peripheral vascular tonus. Hooker[11] stated that local changes in vascular tonus caused no noticeable changes in venous pressure, and he concluded that venous pressure is normally independent of peripheral vascular resistence. The peripheral venous pressure is independent of factors affecting the peripheral vascular system or the blood flow therein, provided the heart is fully competent, as has been pointed out by Eyster and Middleton.[12] On the other hand, it is difficult to regard this fall of the venous pressure below the initial level after exercise as the result purely of some cardiac factor. We have observed it, however, only in cases of heart disease without clinical evidence of congestive failure. We believe that this response of the venous pressure to exercise may be explained by a decrease of the venous tonus in the presence of potential cardiac insufficiency.

In cases in which there was clinical evidence of congestive heart failure, the resting value was usually high, there was a considerable rise on exertion, and it took a longer time to return to the initial level than in normal subjects.

SUMMARY

The venous pressure, if measured only once, with the patient at rest, gives no satisfactory clinical information. The results of measuring the venous pressure during and after exercise enable one to make a more reliable evaluation of the functional capacity of the cardiovenous system.

The air-filled system for measuring the venous pressure with an aneroid manometer is a sound method, and is reliable enough for routine clinical use when technical precautions are strict.

The different types of venous pressure curves which were obtained in the exercise experiments are discussed.

I wish to express my gratitude to Professor Laubry, Head of the Cardiac Clinic, for his constant help and suggestions in the preparation of this paper. I also desire to thank Dr. John Parkinson of London, England, who kindly read the manuscript and made many suggestions for its improvement.

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THE ACTION OF CALCIUM ON THE HUMAN ELECTROCARDIOGRAM

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THE continued response of heart muscle to stimuli depends upon calcium, and excessive amounts of calcium in a perfusion medium will completely suspend relaxation. Billigheimer[1] found that calcium makes the heart's contractile elements more powerful, i.e., that it has an inotropic and also perhaps a bathmotropic effect. After having performed experiments on animals, Kolm and Pick[2] believed that calcium paralyzed the auricles and increased the irritability of the ventricles. The cardiotonic action of calcium was investigated by Danielopolu, et al.,[3] who thought that the diuresis which followed calcium therapy resulted from the action of the drug on the heart, but Loewenberg[4] regarded the diuretic and cardiac effects as independent.

We have studied the action of calcium on the human heart with the electrocardiograph—a method used by Berliner.[5] A 2 per cent solution of calcium chloride was used in most of our experiments, but in some a 10 per cent solution was used. From 45 to 75 grains of the drug were given intravenously over a period of three to twenty-one minutes. The rapidity of administration, or the concentration of the drug in the blood stream, determines the effect. One to four grams of calcium chloride were given intravenously by Ameuille and Rist[6] in treating abdominal tuberculosis. The number of our experiments was limited because of the risk entailed by the doses we used, the difficulty of finding human subjects who were willing to undergo such experimentation, and our own reluctance to subject many to such a procedure.

A fairly constant train of symptoms was observed. The patients complained of intense flushing, or heat, palpitation increasing in intensity, a sense of oppression in breathing, nausea, a metallic taste, profuse perspiration, marked dyspnea, occasional vomiting, faintness, weakness, and a feeling of pressure over the upper sternum, with a dull general headache. Some of these symptoms are to be explained by the dynamic action of rapid intravenous administration.

Reports vary as to the effect of calcium on the blood pressure. We found, uniformly, an elevation of the systolic, and usually a depression of the diastolic, levels. These changes were transient; normal pressures

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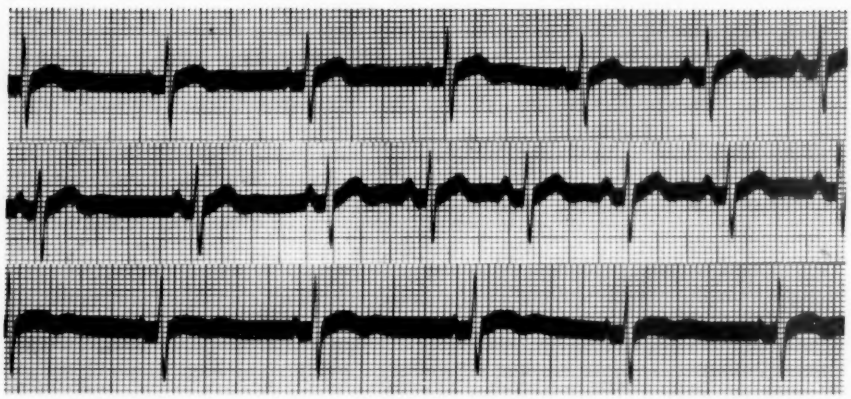

Fig. 1.—Case 1. Electrocardiogram shows sinus arrhythmia, slowing of the rate, and a decrease in the size of the P waves.

Fig. 2*A*.—Case 3. The heart rate is decreased; the P waves become smaller and occasionally are inverted; and ventricular extrasystoles of large voltage, and also auricular extrasystoles, appear. The size of the R waves is much increased; sinus arrhythmia is more pronounced, and the pacemaker shifts to a lower level.

returned within thirty minutes to one hour, and the maximum fall occurred within a few minutes after the administration of calcium was stopped.

CASE REPORTS

CASE 1.—A male physician, aged 34 years, who was in good health and had a normal heart, was the subject of our first and least satisfactory experiment. A total of 40 grains of calcium chloride in a 2 per cent solution was administered intravenously within twenty-one minutes. The appearance of palpitation, faintness, nausea, and vomiting required the discontinuance of the drug. There was no diuresis. The initial blood pressure was 135/80. The systolic readings during the administration of the calcium were 145 and 165, and the diastolic, 70 and 65, mm. Hg. The systolic pressure was 145, and the diastolic, 75, mm. Hg thirty minutes after the administration of calcium was stopped; the readings were normal within one hour. These changes were probably exaggerated by the anxiety associated with the procedure.

A continuous electrocardiographic record (Lead I) was made during the period of calcium administration (Fig. 1).

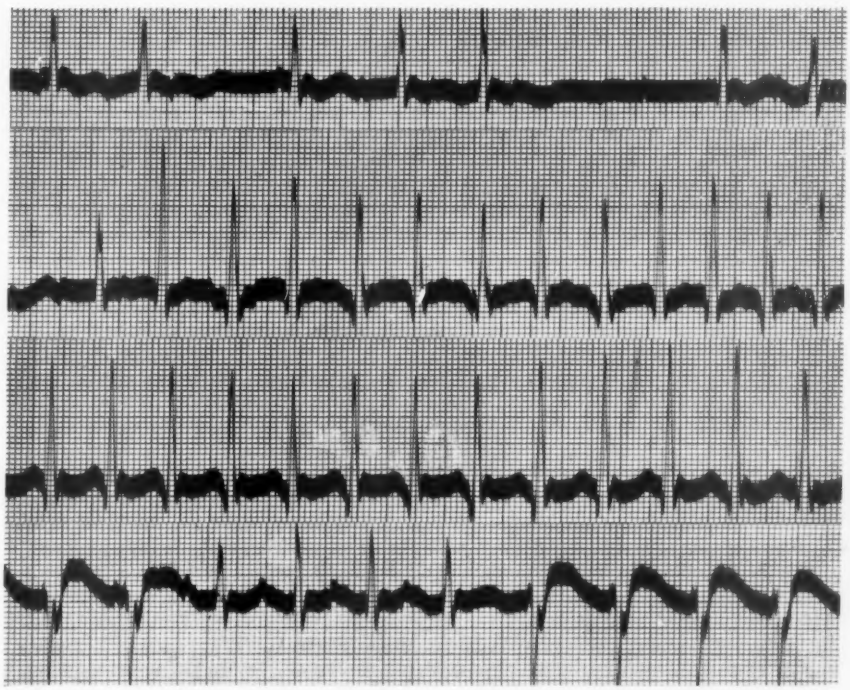

Fig. 2*B*.—Case 3. With further administration of calcium, sinoauricular and A-V block are present. Most of the P waves become inverted, and all are decreased in size. The P-P intervals are shorter, and the apices of the R waves are notched. An independent ventricular rhythm intervenes; the P waves are still present, with occasional ventricular response to the supraventricular stimulus.

CASE 2.—This was a man, aged 40 years, whose general health was good. This patient received 64.5 grains of calcium chloride by vein within eleven minutes. A 2 per cent solution was used. When 22.5 grains had been given, he complained of a metallic taste in his mouth and began to perspire profusely. There was no diuresis.

The normal, resting blood pressure was 95/65. During the injection of the calcium the systolic readings were 115, 125, 130, and 135, and the diastolic, 65, 65, 64, and 70 mm. Hg. Within twenty minutes after the withdrawal of the needle from the vein the blood pressure was 110/70. The electrocardiographic alterations were more pronounced than those shown by the first patient. The outlines were more distinct and the rate was decreased, but sinus arrhythmia was not so evident. The P waves were decreased in size, and became inverted, with a sharpening of their apices.

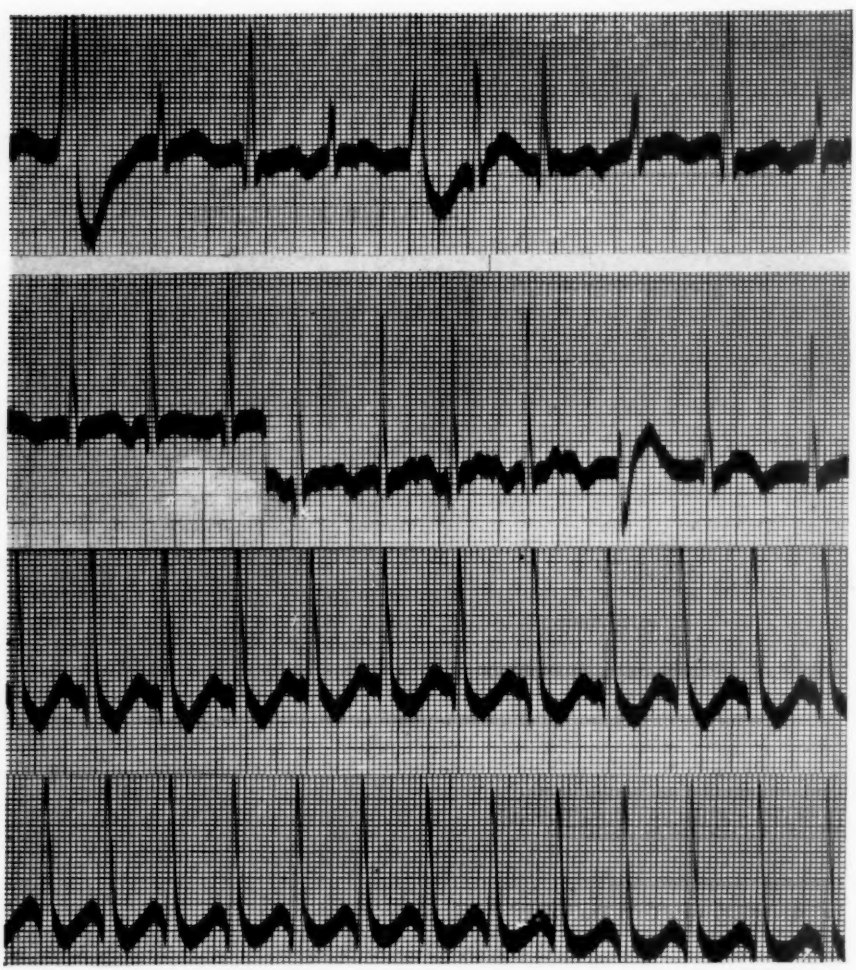

Fig. 2*C*.—Case 3. The heart rate becomes more rapid; the size of the R waves remains much increased, and all evidence of auricular activity disappears.

Case 3.—This patient, aged 45 years, had a chronic discharging sinus on his left leg. The cardiovascular examination showed nothing abnormal. He was given 250 c.c. of a 2 per cent solution of calcium chloride (75 grains) within nine minutes by the intravenous route. There were few symptoms. The tracings are chest leads; Lead II was used for the continuous tracing. The normal, resting blood pressure was 145/90. During the administration of the calcium the systolic readings were

150, 150, 180, and 175, and the diastolic, in the same sequence, were 85, 80, 80, and 75 mm. Hg. The striking changes in his electrocardiograms are shown in Fig. 2*A*, *B*, *C*, *D*.

In Case 3 the heart rate decreased; sinus arrhythmia appeared; the pacemaker was displaced to a lower level; and transient partial and complete heart block was produced. These changes resemble those produced by vagal stimulation. It was observed by Hoff and Nahum,[7] in their experimental work with rabbits, that suppression of vagal action by atropine before the intravenous injection of calcium prevented A-V delay and auricular fibrillation.

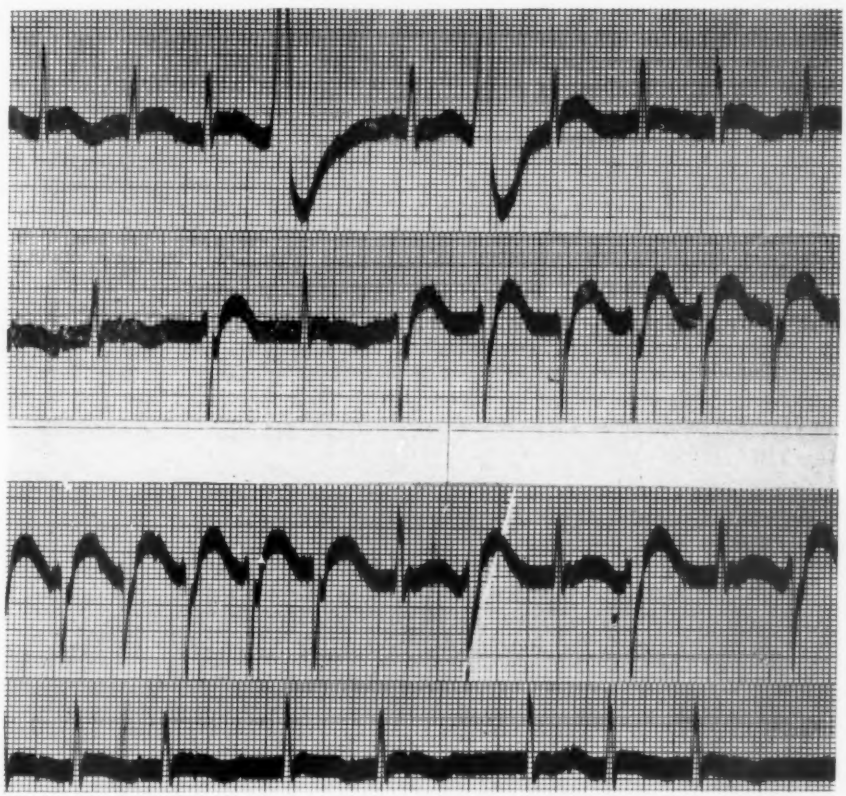

Fig. 2*D*.—Case 3. In the first half of this series the P waves are again evident; some are upright, and others are inverted. In the last half, the idiopathic ventricular rhythm resumes, with a short period of bigeminal rhythm; the extrasystoles are of the same form as those in the paroxysm.

That there is an action on the ventricular muscle seems probable; extrasystoles, usually of large voltage, and series of extrasystoles or paroxysmal ventricular tachycardia occur. This type of extrasystole persists when the vagus is suppressed by atropine, according to Hoff and Nahum,[7] which suggests that increased ventricular excitability is produced by direct calcium action on the ventricular muscle.

In an effort to further differentiate the vagal and direct muscle action of calcium chloride, we administered the drug to a patient with auricular fibrillation.

CASE 4.—A man, aged 47 years, with rheumatic heart disease, had had heart failure with dependent edema, for five months. He had cardiac enlargement, auricular fibrillation, and mitral stenosis. He had received a small amount of digitalis previous to the administration of 45 grains of calcium chloride in a 10 per cent solution, intravenously, within three minutes.

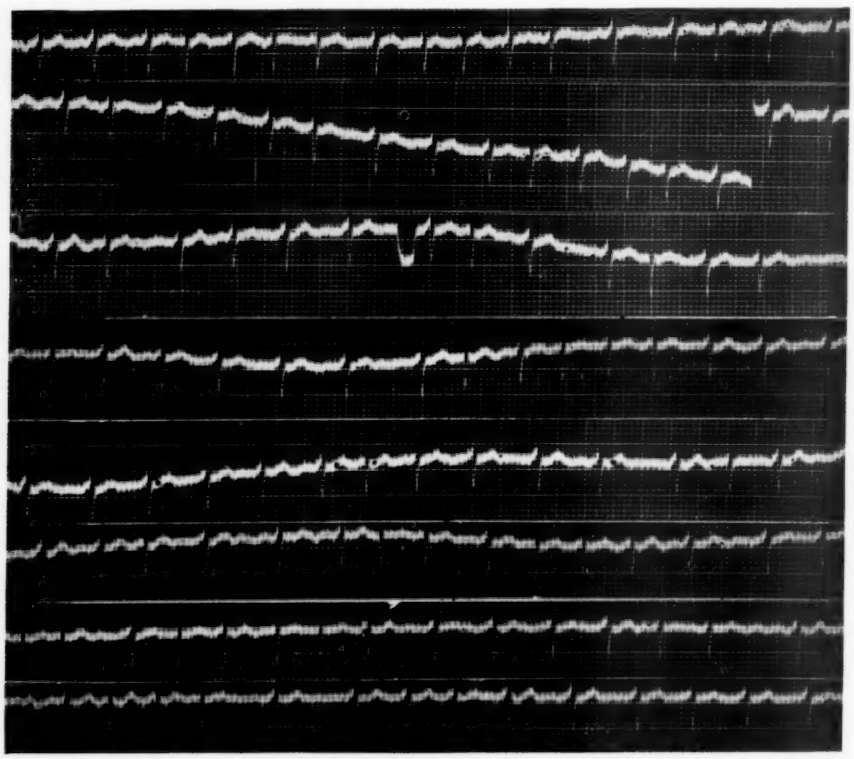

Fig. 3.—Case 4. Lead I was used. This continuous record was taken during intravenous administration of the calcium solution, but no change is noted in the electrocardiogram.

In this single experiment, the calcium had no detectable effect on the electrocardiogram, i.e., the changes which were noted in cases of sinus rhythm did not occur in the presence of auricular fibrillation. A single example does not permit conclusions.

SUMMARY

The intravenous therapeutic use of calcium has advantages and benefits, but carries definite danger.

Calcium produces changes in the human electrocardiogram which are progressive and depend upon the calcium concentration in the blood stream.

The earliest and vagus-like actions are bradycardia, sinus arrhythmia, shifting of the pacemaker, and various degrees of heart block.

Calcium may act directly upon the ventricular muscle, increasing its excitability, and producing foci of idiopathic ventricular rhythm and ventricular extrasystoles of large and unusual form.

The blood pressure was altered; the systolic level was raised, and the diastolic usually was depressed. Accompanying psychic factors and symptoms, such as nausea and chest oppression, could account for some of the change.

We observed no diuresis from calcium administration, and the effects on the heart itself were very transitory.

In the single case of auricular fibrillation the intravenous administration of calcium had no effect on the electrocardiogram.

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EXPERIMENTAL STUDIES ON THE EFFECT OF TEMPORARY OCCLUSION OF CORONARY ARTERIES

II. The Production of Myocardial Infarction

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CLINICAL and post-mortem observations suggest that temporary, relative ischemia in the heart may lead to myocardial necrosis and persistent electrocardiographic changes characteristic of myocardial infarction.[1-4] In cases of angina pectoris caused by coronary arteriosclerosis, small areas of myocardial fibrosis are at times found at autopsy in the presence of narrowing, but without occlusion, of the arteries supplying the affected area. In accord with these observations is the fact that patients during attacks of angina pectoris usually show temporary electrocardiographic changes of the type seen in myocardial infarction.

The experimental investigation reported here was designed to ascertain the duration of the localized ischemia caused by temporary occlusion of a coronary artery which is necessary to produce myocardial infarction in the dog. The effect of temporary myocardial ischemia on the electrocardiogram of the cat has been reported previously,[5] and further electrocardiographic observations on dogs are reported here.

Considerable information is available concerning how long anoxia must last in order to cause permanent damage in various parts of the nervous system[6-8]; almost no exact information is available, however, regarding the period of ischemia required to produce irreversible myocardial changes.

MATERIAL AND METHODS

Temporary arrest of blood flow by occlusion of a coronary artery for 3.5 to forty-five minutes was performed on thirty-four dogs. In five control experiments the same operative procedure was carried out, with the only exception that actual occlusion was not practiced. In two additional dogs a coronary artery was permanently occluded.

From the Medical Research and Pathology Laboratories, Beth Israel Hospital, and the Departments of Medicine and Pathology, Harvard Medical School.

Some of the observations reported herein were presented at the Fifty-Second Session of the Association of American Physicians, May, 1937.

This investigation was aided by grants from the Proctor Fund for the Study of Chronic Diseases, Harvard Medical School, and from the Josiah Macy, Jr., Foundation, New York.

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Operative Procedure.—All operations were performed under aseptic precautions. Anesthesia was produced by intravenous injection of a solution of nembutal in the amount of 35 to 40 mg. of nembutal per kilogram of body weight. In a few animals, small amounts of ether also were required during the course of the experiment.

With the dog anesthetized and on artificial respiration, the heart was exposed through an intercostal incision at the fourth interspace. The left circumflex coronary artery was approached from the right side of the chest; the left anterior descending coronary artery, from the left side of the chest.

A small pericardial incision was made over the site of the artery to be tied. The heart was brought into a favorable operative position by slight traction on hemostats placed on the opened edges of the pericardium. The lung in the immediate operative field was protected during dissection of the artery by a sponge soaked with saline. The coronary artery was carefully and quickly freed from adjacent tissue over an area of 2 to 3 mm., and a No. 2 catgut ligature was slipped loosely beneath it. Veins adjacent to the artery were never included in the ligature. The heart was allowed to drop back into the chest and was kept moist with saline. Traction on the ligature placed beneath the artery was exerted gently to the point of complete occlusion of the artery and was maintained for periods varying from 3.5 to forty-five minutes. Then the ligature was removed and the artery massaged for a few seconds. The color, force of contraction, and degree of dilatation of the heart were observed during the entire procedure. The pericardial incision was sutured in all but the first few animals, and the chest was closed. An injection of 200 to 400 c.c. of 5 per cent glucose in physiologic saline solution was given intraperitoneally.

Leads I, II, and III of the electrocardiogram were taken before operation. In some experiments, additional tracings were taken during various phases of the operative and occlusive procedures. In all cases, the three leads were taken at the end of the operation, again a few hours later, and at intervals of one to three days until the animal was sacrificed. A No. 2 Hindle electrocardiograph was utilized.

The animals were sacrificed from five hours to forty days postoperatively. With the animal under nembutal anesthesia, the chest was re-opened and the heart was removed intact in the pericardium. The pericardium was removed on the dissecting table; adhesions of the pericardium to the heart at or near the operative site were observed in approximately one-half of the experiments, both in the control group and in the group in which temporary occlusion of an artery had been made. In every instance the artery which had been occluded temporarily was carefully probed past the point where the ligature had been passed. The artery and its branches were then laid open as far as possible and examined, frequently under the dissecting microscope. In two animals the lumen of the artery was found narrowed at the point of traction; these experiments were discarded. In the reported cases, including both the control cases and those in which temporary occlusion was practiced, the lumen of the artery which had been temporarily occluded contained no thromboses, fresh or organized, showed no narrowing at the operative site, and the intima was smooth and glistening throughout the entire observable length. Likewise, no obstruction was found in the other main arteries in any animal.

The heart was examined over its entire epicardial surface for macroscopic evidences of pathologic changes, and was laid open for examination of the endocardium. Frequent parallel cuts were then made through the cardiac musculature, and the surfaces of these carefully examined.

Blocks of tissue were removed for microscopic study from the area of the myocardium supplied by the artery which had been temporarily occluded, and also from a portion of the ventricle supplied by another main coronary artery; these latter blocks served as a control.

RESULTS

Control Experiments

In five control experiments the entire operative procedure was performed, with the exception that the ligature, after being placed beneath the artery, was removed after several minutes without occlusion of the vessel. The animals were sacrificed from one to thirty-five days postoperatively (Table I).

Electrocardiographic Observations.—Changes in the direction of the T waves of Leads II and III from upright before operation to inverted in one or more of the postoperative tracings occurred in four of the five control experiments; in the fifth (Dog 68), T_2 and T_3 were inverted preoperatively and showed a greater degree of negativity postoperatively. The S-T segment of Leads II and III changed from the isoelectric level of the preoperative tracings to +1.0 or +1.5 mm. in four of the experiments, and to –1.0 mm. in the fifth (Dog 65). Similar changes have been reported by others.[9, 10] No ectopic beats were observed in any of the tracings.

Morphologic Observations.—No gross or microscopic evidences of cardiac infarction were found in any of the five control experiments (Table I). Further, in none of the hearts were there any evidences of lesions in the control areas supplied by intact arteries.

Temporary Occlusion Experiments

Occlusion of a coronary artery for 3.5 to forty-five minutes was performed on thirty-four dogs. Within the first minute of occlusion of an artery, the myocardium supplied by it appeared cyanotic, and the force of contraction of this area soon diminished. Dilatation of the affected cyanotic area was obvious during the latter part of the longer occlusions. Irregularities of the heartbeat were observed frequently. On re-establishment of blood supply, the affected myocardium quickly resumed its normal color. Normal pulsation and reappearance of normal color of the artery distal to the point of occlusion were observed invariably.

Extrasystoles and Ventricular Fibrillation.—In approximately one-half of the experiments, isolated ventricular extrasystoles occurred during occlusions, or within the first few minutes after re-establishment of blood flow. In several experiments, isolated extrasystoles were seen in electrocardiograms which were taken on postoperative days.

Ventricular fibrillation, with subsequent death, occurred in eight animals; in four of these, fibrillation developed during the first five minutes of occlusion, and, in the other four, within a few seconds after re-establishment of blood flow following occlusions lasting fifteen and thirty minutes (Table I). In seven of these animals the left

TABLE I

EFFECTS OF TEMPORARY CORONARY ARTERIAL OCCLUSION ON DOGS

DOG NO.	ARTERY OCCLUDED	DURATION OF OCCLUSION (MIN.)	PERSISTENT ELECTRO-CARDIO-GRAPHIC ABNORMALITIES*	DURATION OF ELECTRO-CARDIO-GRAPHIC ABNORMALITIES (DAYS)	SACRIFICE OF ANIMAL (TIME POSTOPERATIVELY)	MYOCARDIAL LESIONS	
						GROSS EVIDENCES‡	MICROSCOPIC EVIDENCES
Animals Sacrificed 4 to 40 Days Postoperatively							
14	LC	5	+	4	4 days†	0	
15	LC	10	0		34 days	0	0
17	LC	10	0		40 days	0	0
13	LC	10	+	11	11 days	0	0
7	LAD(B)	20	+	22	22 days	0	0
19	LC	20	+	12	34 days	0	+
21	LC	20	+	2¶	4 days†	0	
22	LC	25	+	10	22 days	+	+
23	LC	30	0		22 days	+	+
3	LAD	30	0		8 days	0	0
9	LAD(B)	30	+	14	14 days	+	+
26	R(B)	35	+	7	13 days	0	+
8	LAD(B)	40	+	18	18 days	+	+
29	LC	45	0		7 days	++	+
27	LC	45	+	10	13 days	++	+
53	LC	45	0		14 days	0	0
54	LC	45	+	14	17 days	++	+
55	LC	45	+	16	16 days	++	+
Sacrificed 4.5 to 28 Hours Postoperatively							
51	LC	15	0		20 hours	Edema	0
52	LC	15	+		28 hours	Edema	0
58	LC	20	0		24 hours	0	0
61	LC	20	0		26 hours	0	+
62	LC	30			4.5 hours	0	0
63	LC	15			5 hours	0	0
69	LC	45			4.5 hours	0	0
70	LC	45			4.5 hours	0	0
Died of Ventricular Fibrillation During Operation							
24	LC	3½					0
18	LC	4					0
59	LC	4½					0
20	LC	5					
12	LC	15					0
28	LC	15					0
50	LC	15					0
10	LAD(B)	30					0
Control Experiments							
65	LC§		0		1 day	0	0
67	LC§		0		1 day	0	0
68	LC§		0		6 days	0	0
66	LC§		0		13 days	0	0
16	LC§		0		35 days	0	0

LC, left circumflex artery; LAD, left anterior descending; R, right artery; B, branch of a main coronary artery.

*In this analysis, + signifies electrocardiographic changes characteristic of myocardial ischemia of a character and degree not observed in control experiments. See text for changes in controls which are tabulated here as 0.

†Animal died.

‡+ signifies one to numerous tiny areas (2 to 4 mm. in diameter) of fibrosis; ++ signifies fibrotic areas of considerable size up to ⅓ left ventricle grossly included.

¶Last electrocardiogram taken before death.

§Ligature placed under artery and withdrawn without occluding artery.

circumflex artery had been occluded, and in one, a branch of the left anterior descending artery. Isolated ventricular extrasystoles during the period of occlusion occurred more frequently in animals which subsequently developed ventricular fibrillation.

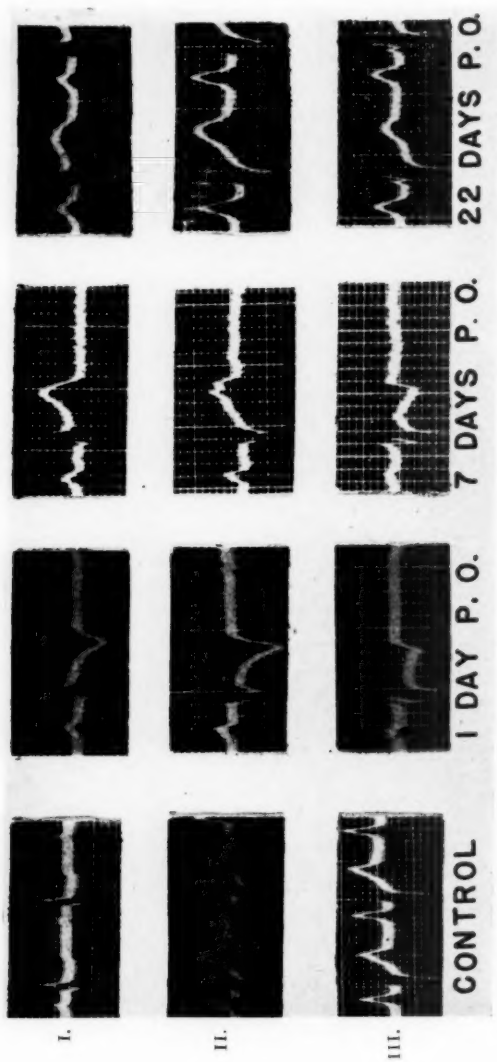

Fig. 1.—Dog 7. Electrocardiograms taken before, and one, seven, and twenty-two days after, a twenty-minute occlusion of a branch of the left anterior descending coronary artery.

Electrocardiographic Changes.—Twelve of the eighteen dogs on which electrocardiograms were made during the postoperative period of four to forty days showed persistent changes typical of myocardial ischemia and different in character and degree from those which occurred in any of the control experiments (Table I). They consisted in more marked aberrations of the S-T segment, with coving, notching, and

other deviations in QRS complexes, and extrasystolic irregularities (Figs. 1, 2, and 3). The maximum changes in the S-T segment usually were observed during the first to fourth postoperative days; the changes persisted for several days to weeks after operation. The type, anterior or posterior, of these electrocardiographic changes varied, depending upon which artery was occluded (Figs. 1, 2, and 3).

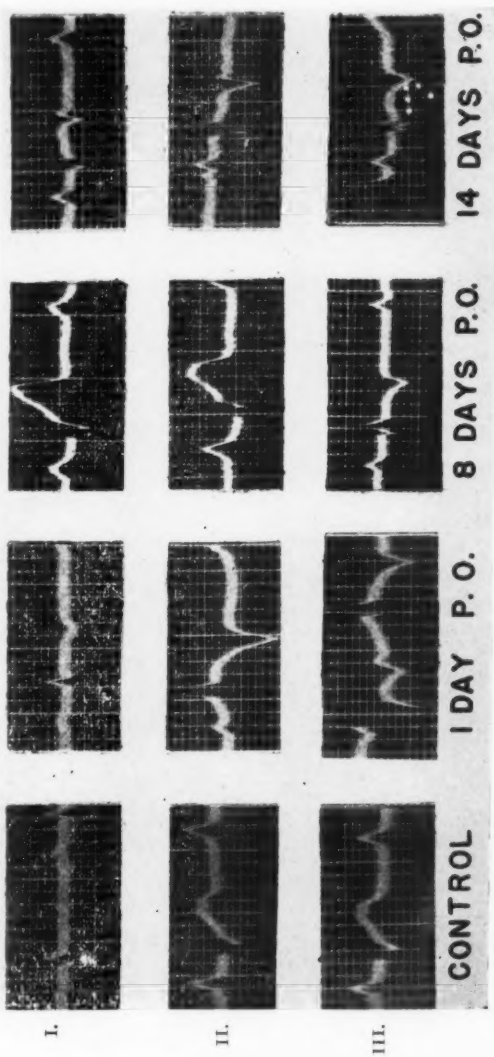

Fig. 2.—Dog 8. Electrocardiograms taken before, and one, eight, and fourteen days after, a forty-minute occlusion of a branch of the left anterior descending coronary artery.

The occurrence of these postoperative electrocardiographic changes was related neither to the duration of occlusion, as produced in these experiments, nor to the presence or absence of an infarct. Although eight of the ten animals which developed myocardial lesions likewise

showed electrocardiographic changes in one or more of the standard three leads, four of the eight whose hearts were free from pathologic changes showed similar electrocardiographic abnormalities. It is important in this connection that all of the animals in which occlusion was produced showed changes in the T wave and S-T segment, but that only the changes which were different from, or much greater than, those observed in any of the control experiments were considered as definitely due to the effects of occlusion.

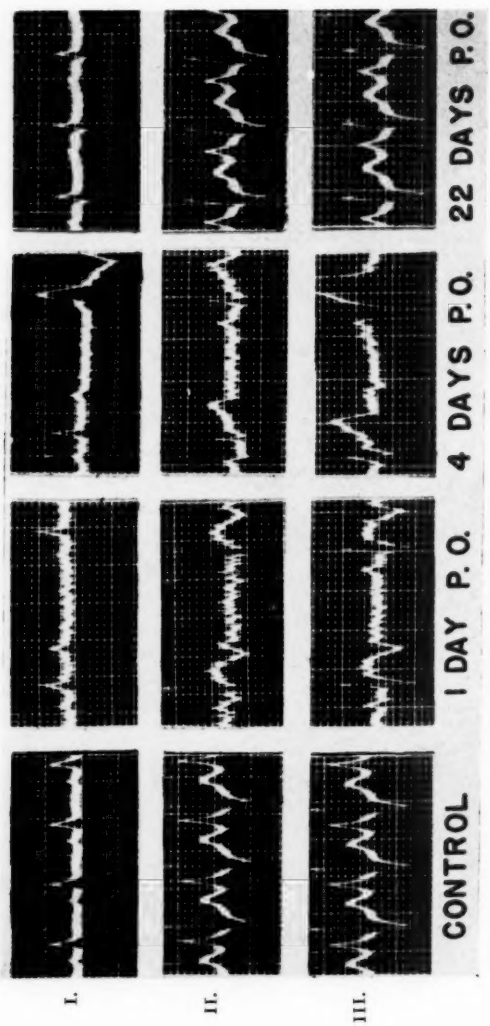

Fig. 3.—Dog 22. Electrocardiograms taken before, one, four, and twenty-two days after, a twenty-five-minute occlusion of the left circumflex coronary artery.

Pathologic Changes.—Myocardial lesions were usually not detectable, either by gross or microscopic examination, in those dogs which were sacrificed from 4.5 to twenty-eight hours after temporary arterial

occlusions lasting fifteen to forty-five minutes. No gross or microscopic evidences of myocardial lesions were found in six of the hearts of the seven dogs which were subjected to temporary occlusion of the coronary artery for twenty minutes or less, and survived for four or more days. In the one exception (Dog 19) the artery had been occluded for twenty minutes, and the animal was sacrificed thirty-four days later. This myocardium showed a few, tiny, fibrotic scars which were detected only microscopically.

Fig. 4.—Dog 8. Photomicrograph of portion of myocardium supplied by a branch of the left descending coronary artery which had been occluded for forty minutes eighteen days before sacrifice of the animal. Note portions of several large areas in a healing infarct, with collapse of the vascular stroma subsequent to the loss of myocardial fibers. These areas are infiltrated with pigment-laden monocytes and lymphocytes. An organized endocardial thrombus is present.

Only two hearts with no evidences of myocardial lesions (Table I, Dogs 3 and 53) were found among the eleven dogs in which the temporary occlusion had been maintained for twenty-five or more minutes and the dogs allowed to survive for seven or more days. In the other nine hearts of this group, myocardial damage was found in the area supplied by the artery which had been temporarily occluded; in one heart, only microscopic lesions were noted (Dog 26); in the other eight

(Table I), the lesions were readily detected on gross examination. In four hearts (Dogs 8, 9, 22, and 23), in which the occlusion had been maintained for twenty-five to forty minutes, the lesions consisted of one to numerous tiny areas (2 to 4 mm. in diameter) of gray, depressed tissue embedded in the myocardium. In the other four hearts (Dogs 27, 29, 54, and 55), however, in which the occlusion had lasted forty-five minutes, an area of considerable size, amounting to as much as one-third of the left ventricle, appeared, grossly, to be involved. Such large regions usually had fairly well-defined borders and appeared swollen, yellowish, and more opaque than the unaffected myocardium.

The gross evidences of myocardial damage were in each instance confirmed by the microscopic examination. In general, the microscopic characteristics were similar to those which are seen after permanent ligation of the coronary artery of the dog. The time relations between the various microscopic changes and the interval after operation agreed closely with those observed by Mallory, White, and Salcedo-Salgar[11] in their study of human cardiac infarcts. The type of lesion which was found after forty minutes of occlusion and eighteen days' survival is shown in Fig. 4. In some of these hearts (Dogs 8, 27, 29, 54, and 55), a lesion was found which the above authors did not describe, and which we have not noted in infarcts in human hearts. This lesion consisted of an outlining by calcium deposition of the structural details of isolated, individual, myocardial fibers.

COMMENT

Myocardial and Electrocardiographic Changes Which Result From Experimental, Temporary, Coronary Occlusion

Previous studies in this laboratory showed that temporary myocardial ischemia in cats, produced by occlusion and subsequent reopening of the left anterior descending coronary artery, causes electrocardiographic changes which persist for days after re-establishment of the blood supply.[5, 12] The postoperative electrocardiographic changes were usually of the anterior infarction type, corresponding to the vessel temporarily occluded, and were similar to those observed during occlusion. As reported here, occlusion of a coronary artery in dogs for periods of five to forty-five minutes also usually caused electrocardiographic changes which persisted for days to weeks; there was no close relation between the degree of electrocardiographic change and the magnitude of the myocardial lesion.

In the earlier studies, none of the cats in which temporary coronary occlusion was maintained for periods of five to thirty-five minutes showed gross or microscopic evidences of cardiac infarction which could be attributed to the temporary ischemia.[5] In many of the hearts of the control cats, as well as of the experimental animals, microscopic examination

revealed small fibrotic lesions scattered throughout the myocardium.[5] For this reason, dogs, in which spontaneous myocardial lesions were not encountered, were chosen for a continuation of these studies. The duration of the arterial occlusion was lengthened, and the postoperative survival period was increased. In dogs, coronary arterial occlusions lasting twenty-five to forty-five minutes usually resulted in grossly detectable myocardial lesions, whereas, after occlusions of twenty minutes or less, gross myocardial lesions were never found, and microscopic fibrosis was found in but one heart. That myocardial infarction did not occur in cats after periods of occlusion similar to those which resulted in lesions in the dog may be due to species differences in the distribution of, and blood flow in, the coronary arteries and their branches.

Tennant, et al.,[13, 14] produced temporary occlusion of a coronary artery and its accompanying veins in dogs, and found that no permanent myocardial damage resulted when the period of occlusion varied from five to thirty minutes, but did find myocardial lesions after two- to eight-hour occlusions. Fauteux[15] has noted that permanent occlusion of a coronary artery in dogs results in smaller myocardial lesions if the veins draining the area supplied by the occluded artery have been previously ligated. The absence of venous congestion in our experiments may explain why myocardial lesions occurred after a shorter period of arterial occlusion than in Tennant's[13, 14] experiments. It is of interest that Bronson[16] found focal myocardial fibrosis in one dog which was sacrificed one month after a coronary artery had been occluded for thirty minutes; in this experiment, as in those of the present study, the veins accompanying the artery were not occluded.

Chemical Changes in the Myocardium

Because of the absence of detectable morphologic alterations in the myocardiums of animals which were sacrificed soon after temporary coronary artery occlusion, studies were made to ascertain whether there might be chemical abnormalities of the affected myocardial tissue. The hearts of eight dogs were examined after occlusions lasting fifteen to forty-five minutes and re-establishment of blood flow for five to twenty-eight hours before the animals were sacrificed (Table I).[17, 18] From the results of quantitative analyses of the sodium, chloride, potassium, and water content of that part of the myocardium supplied by the temporarily occluded artery, it was concluded that these temporary occlusions gave rise early to an extracellular edema amounting to as much as 10 per cent of the volume of extracellular fluid, or that as much as 2.5 per cent of the intracellular phase became permeable to chloride and sodium.[17, 18]

Comparison of the Vulnerability of the Myocardium and of the Central Nervous System to Anoxia

The vulnerability of the myocardium to anoxia, as disclosed by these electrocardiographic,[5] chemical,[17, 18] and morphologic studies, is

strikingly analogous to that of the central nervous system.[6, 19-21, 25] When the myocardium of the cat is deprived of its blood supply, electrocardiographic changes and loss of contractility appear in less than sixty seconds; cerebral anemia lasting twenty seconds obliterates the usual action potentials of the cerebral cortex of the cat.[22] Twenty or more minutes of temporary ischemia are required to produce myocardial necrosis in the dog; this is comparable to the periods of anoxia of ten or more minutes which are required to produce histologic changes in the cerebrum of the cat[7] and to the periods of fifteen or more minutes that are required to produce irreversible changes in the cerebrum of the dog.[23] That various parts of the brain differ considerably in their sensitivity to anoxia has been demonstrated by Heymans and his associates.[20, 21] In contrast to the susceptibility of the heart and central nervous system to anoxia, the intestine can be deprived of its blood supply for as long as three hours without producing irreversible changes in the nerve cells of the myenteric plexus.[24]

Comment on the Relation of Experimental Results to the Clinical and Pathologic Manifestations of Coronary Artery Disease

The above-described experiments were undertaken to elucidate certain clinical problems, as well as to provide information regarding the physiology and pathology of the myocardium. In a recent communication dealing with the relation of the clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathologic findings,[1] it was repeatedly emphasized that the clinical and pathologic data indicated that myocardial ischemia is responsible for cardiac pain. That the heart may recover without structural damage if the duration and degree of ischemia are not too great is amply attested by the symptomatology, electrocardiographic studies, and pathologic findings. If, however, the degree and duration of myocardial ischemia are sufficiently great, irreversible damage, i.e., myocardial necrosis, with its associated symptomatology, results. The duration of temporary occlusion which is necessary to produce structural lesions in the anesthetized normal dog should not be understood as applying quantitatively to the diseased heart of man. The presence or absence of arteriosclerotic narrowing and of collateral circulatory pathways, and conditions such as exercise, anemia, and thyrotoxicosis, in which the heart is performing considerable work, influence materially the degree and duration of ischemia which the myocardium can tolerate. When the cardiac work is increased or the coronary blood supply is decreased, periods of ischemia shorter than those required in our animal experiments would presumably cause myocardial lesions. In man, pathologic observations indicate that inadequacy of the blood supply over a prolonged period of time may cause the same myocardial changes as complete ischemia of shorter duration.[1] In the animal experiments, this concept was substantiated by the fact

that the larger infarcts were produced only by the longer periods of occlusion (Table I), presumably because the peripheral regions of the myocardium which were deprived of their normal blood supply derived an additional supply from neighboring sources.[26, 27]

Experimental, Clinical, and Pathologic Data in Relation to Angina Pectoris.—The focal areas of fibrosis that commonly are found in the hearts of patients with angina pectoris, and in those areas of the hearts of dogs which have been subjected to temporary ischemia for approximately twenty to thirty-five minutes, would seem to have a common underlying pathologic physiologic mechanism. It is the consensus that angina pectoris is the clinical expression of temporary, relative, myocardial ischemia. The electrocardiographic changes during attacks are similar to those induced by the inhalation of low-oxygen mixtures in man,[28] and to those observed in animals in which temporary circulatory arrest is produced by traction on a coronary artery.[29] As noted above, it is not to be expected that a close quantitative relation between the experimental observations and clinical conditions, in respect to duration and degree of ischemia, should obtain.

Experimental, Clinical, and Pathologic Data in Relation to Coronary Failure.—Some patients have cardiac pain more prolonged than that consistent with a diagnosis of angina pectoris, but the clinical evidences of myocardial necrosis, such as fever, leucocytosis, markedly increased sedimentation rate, or progressive electrocardiographic changes over a period of days, are absent. If death, in such cases, is not caused by heart disease, autopsy shows no evidence of myocardial infarction. Since these attacks are more prolonged than those of angina pectoris, and, on the other hand, since the signs of widespread myocardial necrosis are absent, a clinical diagnosis of either angina pectoris or acute myocardial infarction would be erroneous. Coronary failure and angina pectoris seem to have the same physiologic basis, i.e., completely or almost completely reversible myocardial changes caused by ischemia. That these attacks may leave their mark in the form of tiny foci of myocardial necrosis is suggested not only by the pathologic findings, but also by the observations of Riseman and Brown,[30] who found that the sedimentation rate of such patients, while not elevated as much as with myocardial infarction, is nevertheless definitely above the upper limits of normal.

Experimental, Clinical, and Pathologic Data in Relation to "Silent Infarction" of the Myocardium.—Various authors have commented on the finding of infarcts at post-mortem examination in the absence of any history of corresponding clinical phenomena.[2, 31, 32] An inaccurate history as the result of a lapse of memory on the part of the patient, or absence of pain because the patient had been "unsensitive" is frequently postulated. Our experimental results, as well as pathologic observations by one of us (M. J. S.), suggest a somewhat different explanation in certain instances.[1, 33] Some hearts (Blumgart, et al.,[1] Cases 4,

9, 10, 11, 19, and 20) show areas of fibrosis which are larger than the diffusely distributed small foci of fibrosis commonly associated with angina pectoris. These areas generally are regarded as healed infarcts. In most of the instances studied by us, however, the vessels leading to, and within, such areas of marked fibrosis were not completely occluded. Such areas are often quite irregular in outline, and the fibrosis within them has a very patchy distribution. They represent, in some instances, a coalescence of several small areas of fibrosis, such as those which are observed after a single experimental production of temporary ischemia in the dog. The fact that such "infarcted areas" were found predominantly in the hearts of patients with angina pectoris is in accord with these considerations.

The Application of the Experimental Data Obtained in This Study to the Phenomenon of Cardiac Infarction in the Absence of Complete Occlusion of a Coronary Artery in man seems justifiable. As stated above, a sufficient species difference appears to exist between the myocardial blood supply of the cat and dog so that occlusions up to thirty-five minutes were not manifested by pathologic changes in the myocardiums of the cats, whereas occlusions of twenty-five minutes and more caused these changes in dogs. The mechanism whereby massive myocardial infarction is produced by temporary interruption of the blood supply to a part of the dog's heart for forty or more minutes is analogous to that of the occurrence of myocardial infarction without coronary occlusion in man. Myocardial necrosis in man may occur (1) after sudden occlusion of a previously adequate arterial lumen, *before* a fully adequate anastomotic circulation has had an opportunity to develop or, (2) without fresh occlusion of any of the main coronary vessels or their larger branches, under circumstances, such as increased cardiac work, which predispose to prolonged myocardial anoxia. In the hearts of some patients, infarcts, old or fresh, have been found in the absence of any coronary occlusion (Blumgart, et al.,[1] Cases 8 and 28). In other hearts fresh occlusions may be present, but there are no old occlusions corresponding to the old healed infarcts, or fresh infarction may be disclosed without fresh coronary occlusion (Blumgart, et al.,[34] Case 3).

It is in accord with the experimental observations to consider that in a heart with multiple occlusions and narrowings, and thus with an anastomotic but reduced blood supply, slight further narrowing of several blood vessels by any one of several mechanisms, or increased demands on the myocardium because of rapid ventricular rates, effort, etc., may produce a large area of ischemia. This ischemic area may then undergo necrosis, with the production of a large infarct. In several of the cases previously studied, infarction was undoubtedly favored by the fact that these patients did not rest after the onset of occlusion, but continued to work or persist in other activity, thereby increasing the degree and duration of ischemia.

SUMMARY

1. Experiments were performed on thirty-nine dogs to learn whether temporary occlusion of a coronary artery would produce myocardial infarction and persistent electrocardiographic changes characteristic of myocardial ischemia.

2. In twelve of eighteen animals which were allowed to survive four or more days, electrocardiographic changes typical of myocardial ischemia, and of a character not observed in control experiments, were found during the first few days to weeks after occlusion of a coronary artery for five to forty-five minutes. The type, anterior or posterior, of these electrocardiographic changes varied according to whether the anterior descending or left circumflex artery was temporarily occluded.

3. Eight animals died of ventricular fibrillation during the first five minutes of occlusion of the artery, or on re-establishment of the circulation after occlusions lasting fifteen to thirty minutes.

4. No gross evidences of myocardial infarction were found in the seven animals which lived for four to forty days after occlusion of a coronary artery had been maintained for five to twenty minutes.

5. There were gross evidences, proved subsequently by microscopic examination, of infarction in eight of eleven experiments in which occlusion of a coronary artery was maintained for twenty-five to forty-five minutes.

6. In the hearts which showed infarction, the extent of the infarct was roughly in direct proportion to the duration of the arterial occlusion; the infarcted area in several of the hearts in which an artery had been occluded for forty to forty-five minutes was as large as that which occurs after permanent and complete occlusion of the artery.

7. These observations afford evidence that temporary ischemia may cause irreversible myocardial changes, and, if the ischemia be of sufficient duration, may cause myocardial infarction of the same character and degree as that which occurs after permanent and complete occlusion of an artery.

8. The electrocardiographic and myocardial observations on certain patients with coronary artery disease are discussed with reference to the information gained in this study.

We wish to thank Dr. A. Baird Hastings for generously providing facilities which made these studies possible.

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FETAL ELECTROCARDIOGRAPHY

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THE scope of practical electrocardiography can be extended to cover a considerable period of intrauterine life. Heretofore, workers in this field have obtained satisfactory tracings during the eighth and ninth months of pregnancy. The modified technique developed by e of us on (H. M.) consistently yields reliable records from the sixth month of pregnancy to term, and even before the sixth month we have occasionally secured tracings. The application of this technique to a group of forty unselected obstetrical patients and the results obtained form the basis of this report.

HISTORY

The development of the string galvanometer and its successful application in recording the action current of the heart in adults and children led naturally to attempts to obtain fetal electrocardiograms. As early as 1906, Cremer[1] recorded and published fetal electrocardiograms which were taken during the last month of pregnancy. He used two electrodes, one placed in the vagina and one on the abdomen, and his published curves show distinct fetal deflections. This single, early success, however, did not result in any further progress. Attempts to develop a standard method of fetal electrocardiography were unsuccessful because of technical difficulties. The fetal heart was not only small, and, therefore, presumably generated smaller action currents, but it was also separated from the outside by amniotic fluid, fetal membranes, uterus, maternal viscera, and abdominal wall. The application of the electrodes, which presented little difficulty in ordinary electrocardiography, was another problem. Sachs,[2] in 1922, tried to record the electrocardiogram of the fetus in utero by means of abdominovaginal and abdominorectal leads, but he failed to obtain any deflections which could be identified definitely as fetal in origin.

The invention of the audion tube, with the subsequent rapid development of electrical amplifiers, suggested the use of an amplifier to increase the sensitivity of the string galvanometer. Such an amplifier, when properly designed, presented several distinct advantages over the use of the string galvanometer alone. It greatly increased the sensitivity of the instrument and permitted the recording of smaller currents than could be registered with the string galvanometer alone. It simplified the

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problem of skin resistance and permitted the use of smaller electrodes. It eliminated the technical problem of compensating for skin currents, and prevented wandering of the string. By means of such a combination of valve amplifier and string galvanometer, Maekawa and Toyoshima[3] succeeded, in 1930, in recording the action current of the heart of a full-term fetus in utero several hours before birth. They placed the electrodes on the abdomen, and obtained a curve which showed not only the mother's electrocardiogram, but also an independent deflection which corresponded in rate to the fetal heart rate, and which, in the light of later work, notably by Bell,[4] was definitely a fetal electrocardiogram.

The combination of amplifier and string galvanometer, although it had numerous advantages, was cumbersome, difficult to manipulate, and subject to much outside electrical and mechanical interference. Improvements in the string galvanometer and in technique enabled Steffan and Strassmann[5] to obtain a fetal electrocardiogram with this instrument alone, in 1933. In 1938, Strassmann and Mussey[6] reported a series of fifty-two patients who were examined during the last seventy days of pregnancy. Of the seventy electrocardiograms which were taken, sixty-one, or 87 per cent, showed a fetal electrocardiogram, and nine, or 13 per cent, failed to show any discernible fetal curve.

Easby,[7] in 1934, succeeded in obtaining an electrocardiogram of a 4.5-month-old fetus which had been removed from the uterus after hysterectomy, and Heard, Burkley, and Schaefer,[8] in 1936, reported eleven electrocardiograms of fetuses which had been removed from the uterus either by operation or by spontaneous delivery. These curves are valuable and interesting, but have little bearing on the subject of routine, antenatal, fetal electrocardiography.

Johnson,[9] in 1938, published a standard electrocardiogram of a primipara who was almost at term in which fetal deflections were observed and identified. The instrument which he used was of the standard amplifier type, and the recording of the fetal deflections was not intentional. However, the fact that fetal deflections could be observed in an ordinary electrocardiogram, taken in the usual way, suggested that it might be possible to obtain fetal electrocardiograms routinely by a refinement of the technique. The amplifier electrocardiograph had now succeeded in eliminating much of the outside electrical and mechanical interference which had been so disturbing to early workers. In addition, the instrument was portable, and therefore could be carried to the bedside. Furthermore, its standard sensitivity could be doubled by a mere turn of a knob. A preliminary test on several patients indicated that the development of a routine method for fetal electrocardiography was possible.

The technique devised by Mann was standardized as follows. The patient reclines on her back in bed, or on a comfortable couch. Standard electrodes are applied to the arms, near the shoulders, and to the upper part of the left leg. The ordinary three

leads of the electrocardiogram are taken with the amplifier adjusted to give a deflection of 2 cm. per millivolt, or twice the usual deflection. Twenty-five or more beats are recorded in each lead. The electrode on the left leg is then transferred to the upper part of the right leg, and three leads are again taken. Lead I is, of course, the same as the first Lead I. The electrodes are now removed from the arms and leg, and two electrodes are placed on the abdomen in the following six positions: (1) Right upper quadrant, symphysis pubis; (2) epigastrium, symphysis; (3) left upper quadrant, symphysis; (4) right upper quadrant, left upper quadrant; (5) right umbilical region, left umbilical region; (6) right lower quadrant, left lower quadrant.

The right arm wire is attached to the first electrode, and the left arm wire to the second electrode; the lead selector is placed on Lead I, and double amplification is used, as before. Six strips of twenty-five beats each are taken. The first three represent, respectively, the right, central, and left oblique diameters of the abdomen, and the last three are transverse. There is no difficulty in applying abdominal electrodes. A bit of electrode paste is rubbed on the skin. The electrode is applied, covered with a towel, and held in place by the patient's hand, which rests lightly on the towel.

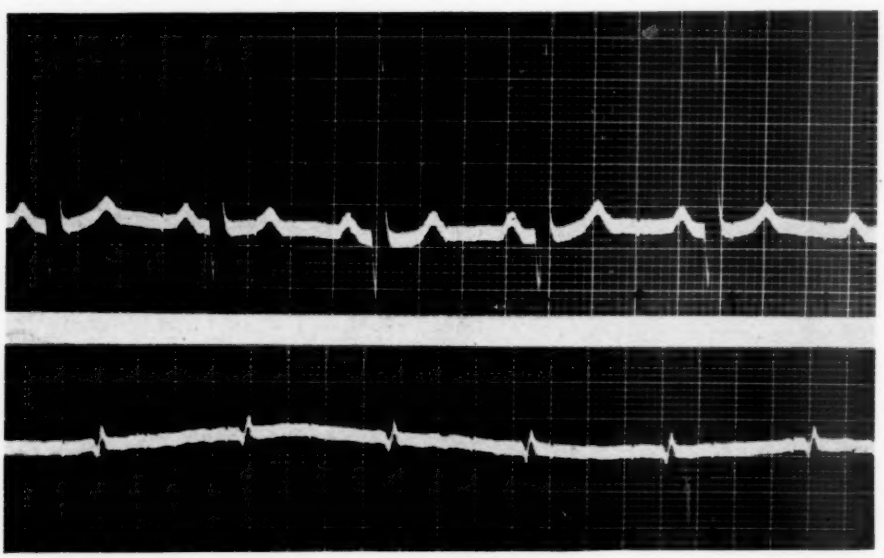

Fig. 1.—Fetal electrocardiograms taken two days before delivery. The upper curve was made with electrodes on the left arm and right leg. The lower curve was taken with electrodes on the abdomen. Standardization of both curves is 2 cm. per millivolt. The arrows indicate fetal deflections.

It will be noted that in this way both limb leads and abdominal leads are taken; this permits a comparison of the value of the two types of external leads which have been advocated for fetal electrocardiography. This comparison is shown in detail later. In general, it may be said that the fetal electrocardiogram, as shown in the abdominal leads, is easier to identify and more suitable for study. The maternal deflections are much smaller in the abdominal leads; the abdominal muscles rarely exhibit tremor, and the fetal deflections are larger than in the limb leads.

The fetal electrocardiogram does not appear equally clearly in all the abdominal leads, but shows considerable variation which is caused probably by changes in the axis of the fetus and anatomic variations in the abdominal organs of the mother. The maternal deflections in the limb leads frequently obscure the much smaller fetal deflections, and, at times, it is very difficult to eliminate small muscle tremors in the limbs.

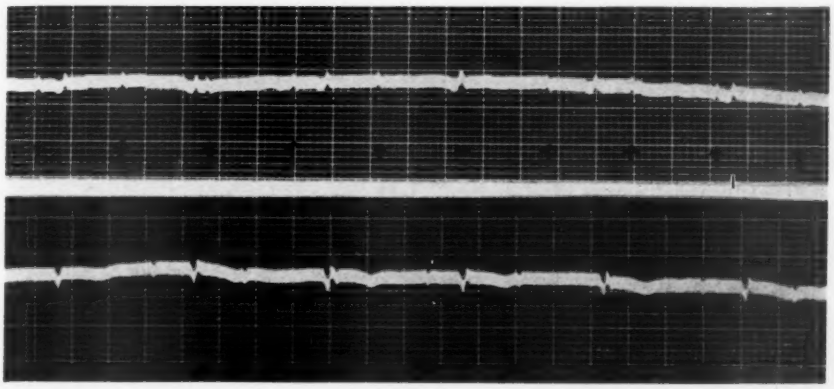

Fig. 2.—Fetal electrocardiogram taken four days before delivery. Two abdominal leads are shown. Arrows indicate fetal deflections.

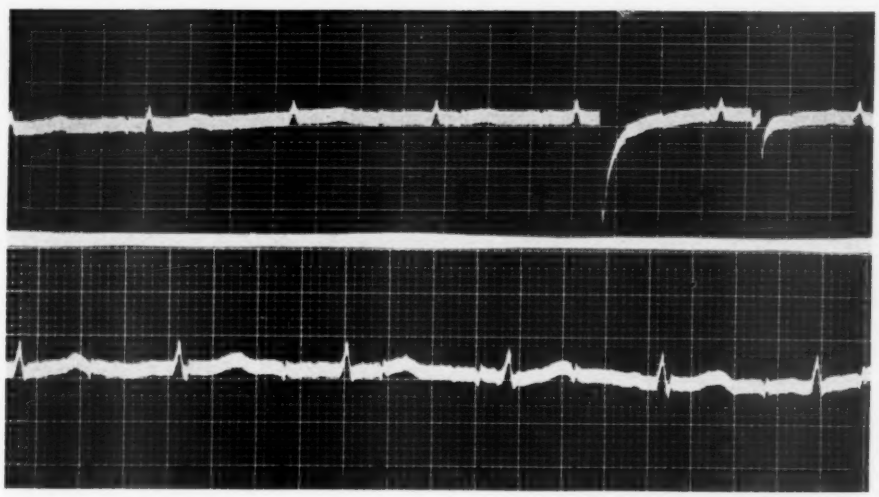

Fig. 3.—Fetal electrocardiograms recorded with abdominal electrodes. The upper curve was taken 128 days before delivery, and the lower curve, 111 days before delivery. The arrows indicate fetal deflections.

Fig. 1 shows a fetal electrocardiogram which was taken in the last month of pregnancy. The upper curve was recorded with electrodes on the left arm and right leg. The lower curve was recorded with one electrode on the epigastrium and the other at the symphysis. The standardization in both curves was the same, namely, 2 cm. per millivolt. It will be noted that, although the fetal deflections are about the same size

in the two curves, they are more easily identified in the lower curve because the maternal waves are much smaller in the abdominal lead.

Fig. 2 shows a fetal electrocardiogram which was taken four days before delivery. Two abdominal leads are shown. The maternal waves are small, and the fetal deflections are readily identified.

The use of abdominal leads permits identification of fetal waves as early as the fifth month of pregnancy. Fig. 3 shows two curves which were taken with the electrodes placed to the right and left of the umbilicus, and recorded 128 and 111 days, respectively, before birth of normal, full-term children.

In exceptional cases, fetal waves have been recorded by us as early as the end of the fourth month of gestation, but the fetal curve is most readily observed during the last 100 days of pregnancy. This is shown in Table I, which is a complete list of our attempts to record fetal electrocardiograms on the forty patients of this series.

The plus and minus signs indicate the presence or absence of a detectable fetal curve. Only those curves in which the fetal deflection could be counted, for at least thirty beats, were considered positive. Doubtful curves were regarded as negative. The numbers indicate the time, in days before delivery, at which the electrocardiograms were taken.

It will be noted that all curves which were taken more than 169 days before delivery failed to show fetal waves and that the proportion of negative curves decreased sharply after the one hundred fiftieth day, so that, by the third month before delivery, many positive curves had appeared. During the last three months of pregnancy, positive curves were the rule, and negative curves, the exception; of the forty patients in our group, thirty-six showed positive fetal electrocardiograms. Of the four patients on whom no fetal curve was recorded, three had electrocardiograms only once, on the one hundred fifty-eighth, one hundred fifty-fourth, and one hundred thirty-seventh days, respectively, before delivery, and the other had two electrocardiograms, on the one hundred seventy-fifth and ninety-sixth days, respectively, before delivery.

A comparison of limb leads and abdominal leads is interesting. Of the thirty-six patients who showed fetal electrocardiograms, twelve had positive curves in the limb leads, and the total number of limb leads in which the fetal electrocardiogram could be identified was twenty-six. Of this same group, thirty-four had positive curves in the abdominal leads, and the total number of abdominal leads in which the fetal electrocardiogram could be identified was 150. Two patients had positive curves only in the limb leads, and twenty-four had positive curves only in the abdominal leads. Ten patients showed positive curves in both limb and abdominal leads. In general, the abdominal leads were definitely superior, both with respect to the number of positive curves, and the ease with which the fetal curve could be identified.

TABLE I

FETAL ELECTROCARDIOGRAMS

CASE NO.	DAYS BEFORE DELIVERY														
1		+20													
2	+6		+41												
3				+51											
4		+24		+52											
5			+31		+59										
6						+68									
7		+26													
8				+46			+83								
9				+41			*-83*								
10						*-78*			+107						
11							+90		+111						
12							+86			*-127*					
13				+43						+128					
14*												+147		*-168*	
15		+21										*-153*		*-175*	
16								*-96*						*-175*	
17			+30									*-150*			
18			+32									*-146*			
19												+148			*-201*
20												+144			*-200*
21	+4		+26						*-110*						
22*									+109						
23													*-158*		
24	+⅓														
25			+26		+47								+157		
26				+38						+126					
27		+21					+74				*-137*				
28			+31							+131					
29	+7				+47						+139				
30		+16				+51							*-162*		
31			+23				*-74*				+137				
32								+89					+165		
33				+39					+107				+169		
34										+133					
35				+39					+111						
36										+117					*-181*
37											*-137*				
38												*-154*			
39										+120					
40*							+78								

\+ indicates that fetal electrocardiogram is present.

– indicates that fetal electrocardiogram is absent.

In forty cases there are fifty-six positive and twenty negative fetal electrocardiograms.

*Delivery premature, calculation approximate.

The relationship between fetal heart rate and sex can be investigated statistically by means of the electrocardiogram. Counts of at least thirty fetal beats gave us the heart rates of those babies in our series whose sex is now known. Stillborn, premature, and abnormal children were excluded. A total of forty-three counts was made in the last five months of pregnancy. Twenty-one of these counts were made on thirteen male fetuses. Twenty-two counts were made on sixteen female fetuses. The rates of the females averaged about 144 beats per minute, and those of the males, about 141 per minute. This difference is insignificant, particularly in such a small series.

TABLE II

FETAL HEART RATES

MALE	FEMALE
138*	124
154	137
137*	151
134	140
142	147*
136	151
144	152*
140	147
134*	154
149*	138
136*	137†
155†	149*
135	158*
	138
	150
	137
Av. 141	144

*Average of two counts.
†Average of three counts.

Fetal electrocardiography may suggest the presence of certain abnormalities in utero, and, for this reason alone, the procedure warrants further study and use whenever unusual conditions are suspected. Not all abnormalities, however, are demonstrable by this means. The results obtained in the following unusual and anomalous conditions are of interest.

In one case[10] of hydramnios and ectopia intestinalis fetalis (gastroschisis), electrocardiograms were made forty-two days and six days before delivery. In both tracings the fetal heart rate was abnormally rapid, and was much faster the second time than the first, thirty-six days earlier. Although the rapid rates suggested fetal distress, the actual condition could not be diagnosed clinically.

A premature, living baby which was delivered in the seventh month of pregnancy showed no abnormalities of the heart rate in a tracing taken forty-nine days before delivery. Birth weight was 3 pounds, 13 ounces.

TABLE III

FETAL AND MATERNAL HEART RATES AT DIFFERENT PERIODS BEFORE DELIVERY

RATE	DAYS BEFORE DELIVERY																
	0 TO 9	10 TO 19	20 TO 29	30 TO 39	40 TO 49	50 TO 59	60 TO 69	70 TO 79	80 TO 89	90 TO 99	100 TO 109	110 TO 119	120 TO 129	130 TO 139	140 TO 149	150 TO 159	160 TO 169
Fetal	131		124	144	134	137	140	143	140	148	142	146	158	150	147	162	149
Maternal	89		78	79	78	80	105	76	63	81	94	73	92	83	108	84	75
Fetal	138		139	140	134	136			151		151	138	152	138	154		171
Maternal	89		111	93	93	89			87		89	86	92	85	94		75
Fetal			154	147	146	151			167			150	137				
Maternal			106	95	88	71			78			75	69				
Fetal			136	148	124												
Maternal			64	98	95												
Fetal			137	144													
Maternal			90	86													
Fetal			125	132													
Maternal			94	77													
Fetal			129														
Maternal			71														
Fetal (Av.)	135		135	143	135	141	140	143	153	148	147	145	149	144	151	162	160
Maternal (Av.)	89		88	88	89	80	105	76	76	81	92	78	84	84	101	84	75

A premature, stillborn infant which was delivered in the eighth month of pregnancy had a normal heart rate fifty-seven days before delivery. Birth weight was 4 pounds.

In a recent case in which the obstetrician was uncertain as to whether or not the child was alive, an electrocardiogram failed to reveal fetal deflections. Two days later, an 8-month-old, macerated fetus was delivered.

One patient had twins; the first to be born was a male which occupied the right occipitoanterior position, and the other, a female, lay transversely in the fundus. Electrocardiograms which were taken sixteen and fifty-one days before term revealed an excellent record of but *one* fetus. Re-examination of the curves failed to reveal a second fetal electrocardiogram.

The electrocardiogram of a full-term baby which died twelve hours after birth from multiple heart lesions (autopsy confirmation) was normal twenty-three days and 137 days before delivery. The anomalies consisted of patent foramen ovale, absent interventricular septum, single arterial trunk (aorta), with pulmonary arterial branches, hypoplasia of the mitral valve, and opening of a rudimentary mitral orifice into the right ventricle. Re-examination of the fetal electrocardiogram failed to disclose any abnormality.

The relation of the fetal heart rate to the age of the fetus, as well as to the maternal heart rate, is subject to exact study by this method. Table III shows the fetal and maternal heart rates in our cases during the last five months of pregnancy. The rates were calculated by counting the number of beats recorded in twelve to twenty seconds of continuous recording. There did not seem to be any constant or obvious relation between the fetal and the maternal heart rate, but there was a slight tendency for the fetal rate to be more rapid early in pregnancy.

In counting the fetal heart rate it is often possible to observe temporary changes in rate corresponding to the sinus arrhythmia of adults. We observed changes in the fetal rate during periods of relative anoxemia caused by paroxysmal tachycardia in the mother. The effect of administering drugs to the mother, and of tobacco smoking, may be studied by this method.

The relationship between the position of the fetus and the character of the fetal electrocardiogram is of interest. Until the last month of pregnancy the fetal position is not fixed, so that attempts to ascertain the position by the contour of the electrocardiogram have little practical value. During the final month of pregnancy the fetal presentation is generally determined, and can be readily ascertained by the commonly used obstetrical methods. With the usual vertex presentation, the direction and shape of the fetal deflections correspond to what we expect to find, bearing in mind the positions of the electrodes and the fact that

the fetus is inverted. The fetal deflection is generally diphasic, but because of its small size few details can be observed. During the latter part of our investigation, the laboratory which manufactures the electrocardiograph which we employed submitted for experimental use an instrument with increased amplifying power. With this new instrument an amplification of about 5 cm. per millivolt was readily obtained. With such amplification it should be possible to study more closely the shape of the fetal ventricular complex.

SUMMARY AND CONCLUSIONS

1. A modified technique of fetal electrocardiography is presented, with illustrative curves. Abdominal leads were found to be superior to limb leads.

2. The history of fetal electrocardiography is briefly sketched.

3. The method has limitations and shortcomings which are still to be eliminated.

4. Of significance was the large number of satisfactory tracings which were obtained during the last trimester of pregnancy, namely, 90 per cent, or thirty-six of forty curves. The earliest clearly defined curve was obtained on the one hundred sixty-ninth day before term (during the fourth month of gestation). As far as we are aware, no fetal electrocardiogram has ever been obtained earlier than this.

5. In some cases, fetal distress or death in utero can be definitely diagnosed.

6. Fetal anomalies and congenital heart disease, per se, do not reveal themselves electrocardiographically.

7. From the observations so far, sex cannot be prognosticated. Conclusions from a larger study will soon be forthcoming.

8. There is no obvious relationship between the fetal and maternal heart rates. Fetal rates are generally more rapid early in pregnancy.

9. The relationship between the fetal position in utero and the size and shape of the electrocardiographic deflections, fetal arrhythmias, and drug effects on fetal rate can be studied accurately by this method.

10. The effects of maternal anoxemia, as well as sinus arrhythmia, upon the fetal rate have been observed.

11. The diagnostic possibilities of the technique described should be investigated further.

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THE WOLFF-PARKINSON-WHITE SYNDROME, WITH PAROXYSMS OF VENTRICULAR TACHYCARDIA

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A PECULIAR syndrome was first described by Wolff, Parkinson, and White[1]; it consists of a short P-R interval and bundle branch block in the electrocardiogram, and it occurs in patients who have paroxysms of tachycardia, but are otherwise apparently well. There have since been other reports of similar cases, in all of which there is a fairly uniform pattern. Although isolated cases of a somewhat similar type were previously reported by Wilson,[2] Wedd,[3] and Hamburger,[4] it was not until the publication by Wolff, et al., that the condition was really called to the attention of the medical profession. The syndrome is unique, and therefore deserves to be regarded as a clinical entity. For the present, because of the difficulty in describing the condition in a simple expression, it might be termed the "Wolff-Parkinson-White Syndrome." When it was first described, it was pointed out that these patients have attacks of tachycardia, for the most part of auricular origin, and, less frequently, paroxysmal auricular fibrillation. One peculiarity was that, while the heart was beating slowly and normally, the P-R time was short (0.08 to 0.10 second) and the QRS interval was markedly increased (0.10 to 0.12 second), whereas, during paroxysms, when the rate was rapid, the QRS interval was normal. It was also noted that these patients showed spontaneous reversion to normal P-R and QRS intervals without an attack of tachycardia or as a result of atropine administration. It is of interest that in the majority of the previously reported cases the patients were males; this sex discrepancy also prevails in ordinary, benign, paroxysmal auricular fibrillation.[5]

The mechanism of this abnormality is by no means clear; various hypotheses have been suggested. The appearance of the ventricular complexes is like that of bundle branch block, and the short P-R interval makes one wonder whether the pacemaker is in the A-V junctional tissue. Wolferth and Wood[6] discussed the possibility that the impulse may reach the ventricles from the auricles through an abnormal pathway, the so-called bundle of Kent. It is not the purpose of this paper to discuss theories concerning the mechanism involved, but rather to report three additional cases in which there were unusual features.

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In practically all of the previously reported instances of this syndrome, when the paroxysms were identified, they were found to be auricular in origin, i.e., either tachycardia or fibrillation, but our three patients had paroxysms of *ventricular* tachycardia. Only two such cases have so far been reported.[7, 8] As will be seen below, these attacks occurred in patients who had no other evidence of organic heart disease; they all showed characteristic electrocardiograms when the heart rate was slow and curves typical of ventricular tachycardia when the rate was rapid. In order to emphasize some practical and clinical aspects of this condition that may not be fully appreciated, a fourth case, in which the paroxysms were of auricular rather than ventricular origin, is discussed.

CASE 1.—S. G., (Med. No. 55244), a 13-year-old white boy, was admitted to the Medical Service of the Peter Bent Brigham Hospital in the evening of June 6, 1939, complaining of pain in the chest and shortness of breath of seven hours' duration. He had had whooping cough and mumps at an early age and measles at 10. There was no other history of infections. His growth and development had been entirely normal. On the day of admission he had played as usual, and felt perfectly well until 7:00 P.M., when, while standing quietly, he suddenly felt weak and breathless. He gradually developed an aching pain beneath the sternum, and vomited. He was put to bed. The patient stated that he "felt as if his heart was pounding all over his body." A physician who was called attempted to stop the attack by carotid sinus pressure. This gave no relief, so that a hypodermic injection was administered, and he was brought to the hospital 4½ hours after the onset.

On admission to the hospital his temperature was 98.6° F.; his pulse was weak, thready, and irregular, and the rate at the wrist was about 80 per minute. The respiratory rate was 30 per minute. The blood pressure readings were unsatisfactory; some beats were audible at 95 mm. Hg, and others were heard down to 80 mm. Hg, but none below that level. The patient was a well-developed and well-nourished boy who appeared to be somewhat more than 13 years of age. He insisted on sitting upright, gasped for air, and complained of pain beneath the sternum. The lips and nail beds were cyanotic; the skin was pale, cool, and moist. The neck veins were not distended. Examination of the heart showed that the apex impulse was rather forceful and diffuse, and lay 9 cm. from the midsternal line. No thrills were felt, and there was no cardiac dullness to the right of the sternum. The heart sounds were described as follows: "The first sound at the apex was very loud, and the rate was extremely rapid. The rapid rate caused the heart to sound like the firing of a machine gun; a long period of regularity was followed by gross irregularities. The second sound was not remarkable, and no murmur was heard." The heart rate could not be counted accurately, but was said to be more than 200. The lungs were normal. The abdomen showed no tenderness or rigidity, and no mass was felt. The remainder of the physical examination revealed nothing remarkable. The leucocyte count was 9,000, and the urine was negative. The electrocardiogram showed ventricular tachycardia (Fig. 1). The patient was given morphine, which made him drowsy and more comfortable. He was also given 2.0 c.c. of digalen intramuscularly, without effect. Pressure on the eyeballs and on the carotid sinuses had no effect. He was then given 0.2 Gm. of quinidine sulfate orally. Forty minutes later his cardiac rate was found to have slowed to 80 per minute, and the rhythm was normal. An electrocardiogram at that time showed a short P-R interval and defective intraventricular conduction. The temperature rose to 99.6° F. by mouth on the second day.

There was no return of the tachycardia during the next seven days in the hospital. Since that time the patient has taken 0.2 Gm. of quinidine sulfate, daily, as a prophylactic measure, and has been seen from time to time. The electrocardiograms have shown little change. A roentgenogram at the time of his hospital admission, and another, one year later, showed no cardiac enlargement or abnormality in outline.

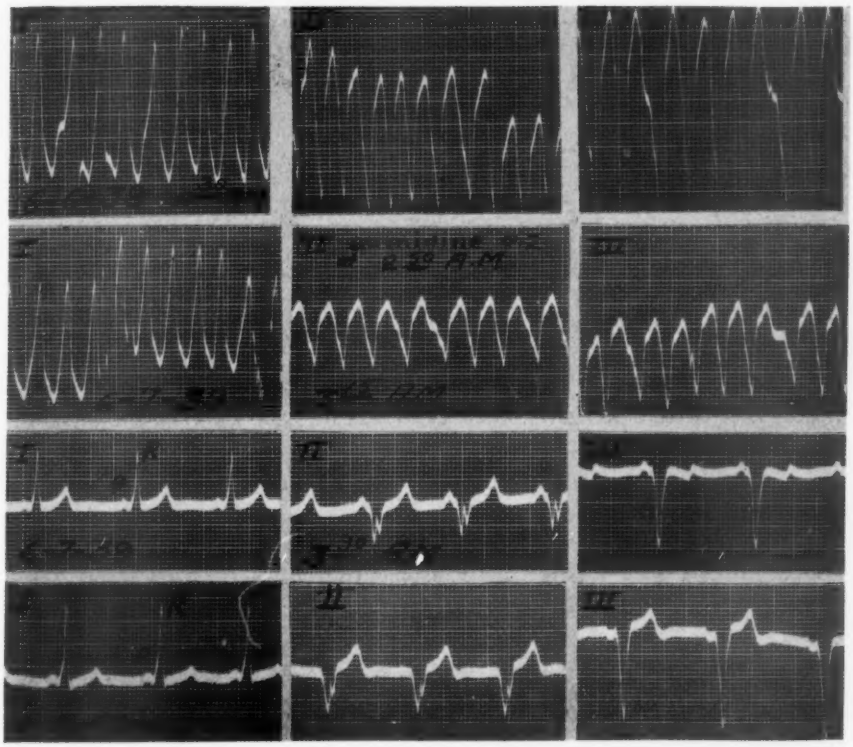

Fig. 1.—Case 1. First tracing shows ventricular tachycardia, with a rate of 292. Second tracing (twenty-five minutes after oral administration of 0.2 Gm. of quinidine) shows slowing of ventricular rate to about 225. Third set (forty minutes after administration of quinidine) shows slow normal rate. Note short P-R and long QRS intervals. Lowest set, taken seven months later, shows same mechanism.

Comment.—This patient had the typical electrocardiograms described by Wolff, et al., but the paroxysm of tachycardia was ventricular in origin. It is of importance that the attack, which was quite serious, was refractory to all the measures employed for paroxysms of auricular origin, but apparently responded promptly to quinidine. He has had no recurrence and has been taking quinidine regularly.

CASE 2.*—A 40-year-old white man, an office worker, was first seen in December, 1937. He complained of general malaise, headaches, insomnia, and a capricious appetite for the preceding six months. In addition, he had had a number of attacks of palpitation during that period of time. These attacks were not accompanied by

*We are greatly indebted to Dr. James B. McLester, of Birmingham, Ala., for giving us the data in this case.

pain or dyspnea, but he felt obliged to sit down and rest while they were present. They usually lasted about five minutes. Physical examination revealed no significant abnormalities. The heart was not enlarged; the sounds were normal; and there were no murmurs. The rhythm was normal and the rate was 90 per minute. The blood pressure was 100/60. A roentgenogram of the chest showed no cardiac enlargement and normal lung fields. Roentgenograms of the skull, sinuses, and gastrointestinal tract showed nothing abnormal. There was no anemia; the total and differential leucocyte counts were normal. The blood Wassermann reaction was negative. Urinalysis revealed nothing abnormal. There was free HCl in the gastric juice. The basal metabolic rate was normal. The electrocardiogram showed short P-R and prolonged QRS intervals, but otherwise was not remarkable.

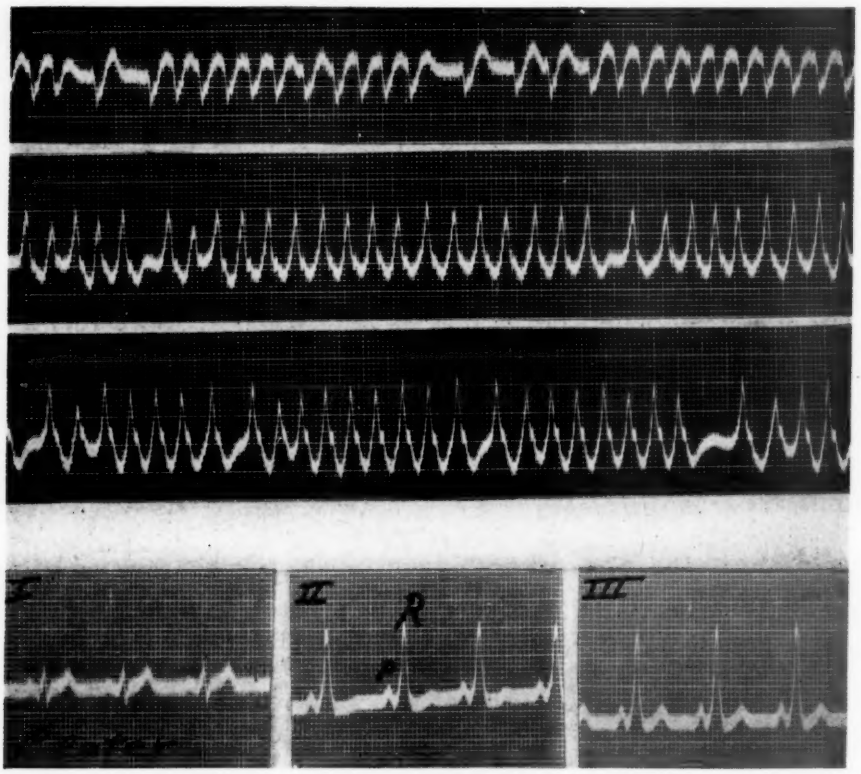

Fig. 2.—Case 2. Upper three leads show typical ventricular tachycardia; rate is 246. Lower set, one hour later, shows slow regular rate, with short P-R and prolonged QRS complexes.

Two days later the patient began to have palpitation in the evening, and the attack persisted until the next morning, when he returned to his physician's office. Examination showed that the heart rate was extremely rapid and could not be counted. At the wrist only 25 to 50 pulses per minute could be felt. The electrocardiogram which was taken at that time showed ventricular tachycardia (Fig. 2). One hour later the attack ceased spontaneously. Immediately after cessation of the attack another electrocardiogram was taken. This showed the same short P-R interval and prolonged QRS complex.

Unfortunately, this patient did not return for a follow-up examination, so that there is no information available as to his subsequent course.

Comment.—This case also belongs to the group with short P-R intervals and prolonged QRS complexes, but here again the paroxysm of tachycardia was of ventricular origin.

CASE 3.*—L. L. was a 36-year-old steamfitter who had always been in excellent health until the onset of an attack of tachycardia. This occurred at 8:30 A.M., Dec. 4, 1939. While lifting a heavy box, he suddenly became conscious of a "knock"

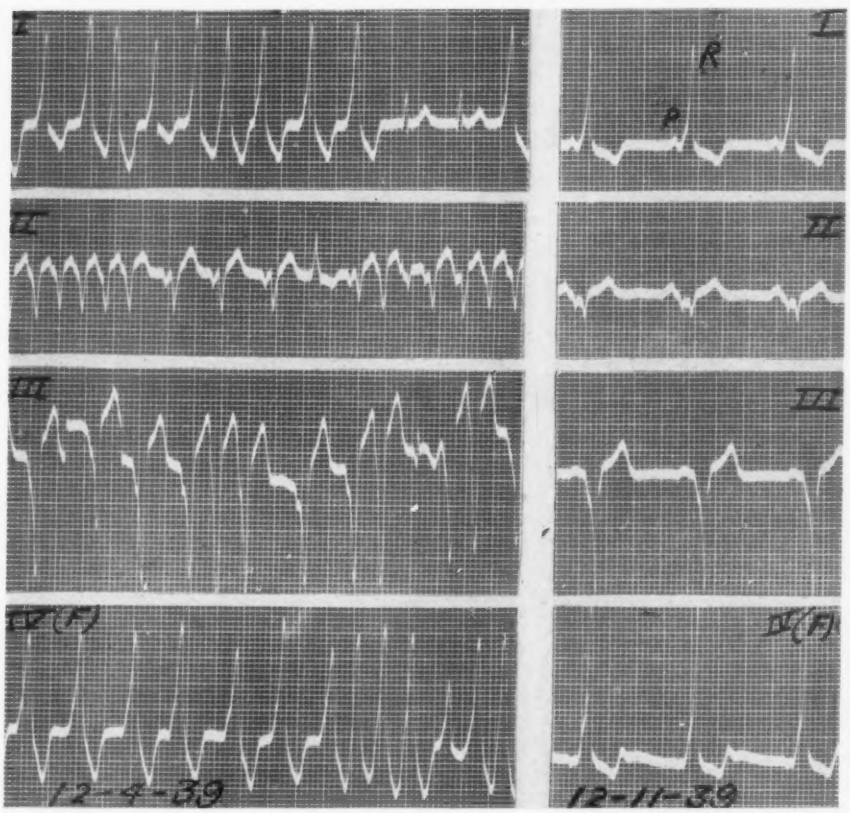

Fig. 3.—Case 3. Tracings on left show ventricular tachycardia, with occasional supraventricular beat; rate is 208. Set on the right shows slow regular rate, with short P-R and prolonged QRS intervals.

in the center of his chest, accompanied by dyspnea and extreme weakness; there was no real pain. He was transported to a hospital thirty miles away by automobile. On admission to the hospital he was found to be flushed but not dyspneic, and apparently in no great distress. The pulse rate was very rapid, and the heartbeat, totally irregular. The blood pressure was 115/75. The temperature was 99.2° F. (rectal). The electrocardiogram which was taken at that time showed ventricular tachycardia (Fig. 3). The tachycardia persisted until evening. At 11:00 P.M. he was given 0.8 Gm. of digitalis orally. At 2:00 A.M. the next day it was found that his heart rate had slowed to 96, with normal rhythm. Examination of the blood later that day showed no anemia; the leucocyte count was 14,700,

*We wish to thank Dr. T. F. Brewer of Hartford, Conn., for giving us some of the data in this case.

with 78 per cent polymorphonuclears. The electrocardiogram showed the characteristic, short P-R interval and bundle branch block (Fig. 3). The leucocyte count was 18,000 on the second hospital day, and during the remainder of his stay in the hospital it was 13,000 or 14,000. He was afebrile at all times. On December 8 a consultant examined him and noted that he was a thickset, muscular man who appeared perfectly well and had no complaints. The heart was not enlarged; the sounds were of good quality; the rhythm was normal; and the rate was 80 per minute. The blood pressure was 142/90. The lungs were normal. It was decided to treat the patient as if he had had a myocardial infarction; accordingly, he was kept in bed in the hospital for six weeks.

On Jan. 31 the patient was seen by one of us (S. A. L.). Physical and routine laboratory examinations showed nothing remarkable. The electrocardiogram was similar to the previous tracings. Roentgenologically, the lungs and heart were normal; the transverse diameter of the heart was 13.9 cm., and that of the chest was 29.8 cm. It was considered probable that the patient had not had infarction, and that all of the symptoms could be attributed to an attack of ventricular tachycardia. Consequently, it was advised that he be allowed to resume his work as a steamfitter, under the observation of his own physician. This was done, and, up to the time of this writing, there has been no untoward occurrence.

Comment.—This is another case of short P-R and lengthened QRS intervals, with an attack of tachycardia of ventricular origin. Because the latter occurs in acute coronary thrombosis, and because of the fall in blood pressure and the presence of a leucocytosis, an erroneous diagnosis of myocardial infarction was made. It is most likely that this patient has no organic heart disease, and that the prognosis is very good.

CASE 4.—S. O. S. (Med. No. 47703). This man was first seen on Oct. 22, 1935. He was a powerful man and was employed as a director of athletics. There was no history of rheumatic fever, chorea, venereal disease, or hypertension. A brother is known to have had transient auricular fibrillation without heart disease. Beginning six years earlier, he had had attacks of palpitation which came and ended suddenly, usually during effort, such as playing handball, and lasted about fifteen minutes. He would quickly resume his activities after an attack. At first he thought that the heartbeat was rapid and regular during the attacks, but later, for several years, he felt that the beating was irregular and that the attacks lasted longer. He had been given digitalis and quinidine at different times, but finally became dissatisfied with physicians and took no medication. Despite this he carried on all his duties satisfactorily until August, 1935, when breathlessness on exertion and fatigue, which he had never experienced before, appeared. This grew worse, so that he finally noticed shortness of breath at rest; his weakness increased, and he had to quit his work. It was later learned that a physician had found his heartbeat grossly irregular several months before, and the patient thought that it had been constantly irregular for about six months.

Physical Examination.—The patient was a large, muscular man. The blood pressure was 96/80. The heart was slightly enlarged; the beating was absolutely irregular; the rate was about 130; and there were no murmurs. There were a few râles at the bases of both lungs. The liver was not enlarged, and there was no peripheral edema. The vital capacity of the lungs was 3,900 c.c.

The diagnosis was auricular fibrillation (cause unknown). He was studied at the Peter Bent Brigham Hospital, where the same observations were made. The blood Wassermann reaction was negative. The leucocyte count was 21,900; the urine

and stool were negative. The basal metabolic rate was -13 per cent, and there was no fever. Roentgenologic examination on Oct. 24, 1935 (while he had auricular fibrillation), showed pulmonary congestion and moderate cardiac enlargement, with no prominence of the left auricle. The transverse diameter of the heart was 17.7 cm. On Oct. 31, 1935, when the cardiac mechanism was normal, roentgenograms showed clearing of the lungs and a transverse cardiac diameter of 16.8 cm.

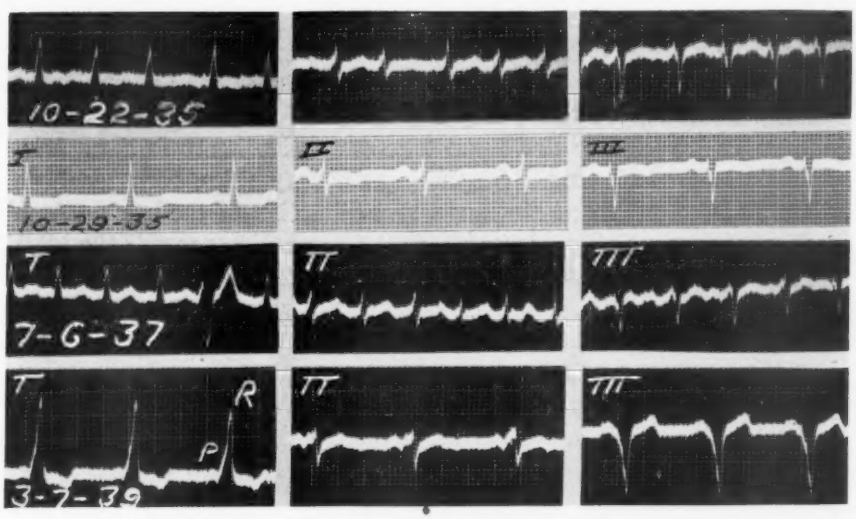

Fig. 4.—Case 4. Upper and third set show auricular fibrillation. Second set shows normal slow rate, with normal P-R and QRS intervals. Lowest set shows slow regular rhythm, with short P-R and prolonged QRS intervals.

He was given 1.6 Gm. of digitalis during the first two days. The auricular fibrillation continued, but the ventricular rate slowed to about 80. Although he felt much improved, quinidine therapy was started. On the third hospital day he received 0.3, 0.5, and 0.5 Gm. of quinidine at four-hour intervals. The next day he was given 0.7 Gm. in the forenoon and 1.0 Gm. in the afternoon. The fibrillation continued, and the heart rate accelerated considerably. The following day he received 1.0 Gm. four times at four-hour intervals. One hour after the last dose he suddenly became unconscious and had urinary incontinence. He was treated for shock, and was given 0.5 Gm. of caffeine sodium benzoate; in a short time he recovered and appeared to be in good condition. The heartbeat was then found to be slow and regular. During the same day he also received 0.3 Gm. of digitalis. After normal cardiac mechanism had been restored, he was kept on a maintenance dose of 0.2 Gm. of quinidine t.i.d. His improvement was striking; the vital capacity of the lungs rose to 4,800 c.c., all symptoms disappeared, and he returned to his former life of strenuous physical activities.

He has carried on very well during the past five years. At first there were occasional attacks of palpitation which lasted a few minutes, and during a few of these he fainted. Because long periods elapsed when he had no attacks, he had reduced the dose of quinidine to 0.2 Gm. once daily. On one occasion, in March, 1939, an attack of fibrillation lasted for about one week, and he had to take digitalis for a few days, followed by increasing doses of quinidine, to obtain reversion to normal rhythm. Since then, on two doses of 0.2 Gm. of quinidine daily, he has done very well. A roentgenogram on June 3, 1939, showed perfectly normal lungs; the transverse diameter of the heart was 14.8 cm.

Comment.—The electrocardiogram (Fig. 4) shows that this case also belongs to the group with short P-R intervals and prolonged QRS complexes. The attacks of palpitation in this case were of the customary auricular variety; at first he probably had paroxysmal auricular tachycardia, but later it was paroxysmal auricular fibrillation. The important point in this case is that, whereas the latter attacks always lasted only a few minutes, were not incapacitating, and occasionally were accompanied by syncope, he finally developed persistent fibrillation. As a result of the uncontrolled rapid heart rate during months of auricular fibrillation (he was not taking any digitalis), while he was trying to continue an active life, he developed true congestive heart failure. The manifestations of this were dyspnea, pulmonary râles, roentgenologic evidence of congestion of the lungs, and dilatation of the heart. As a result of treatment all evidence of heart failure disappeared; the vital capacity rose from 3,800 to 5,000 c.c.; the transverse cardiac diameter diminished almost 3 cm.; and he has shown no evidence of organic heart disease all these years. This experience demonstrates that, when the heart is normal, heart failure may be brought about by prolonged overwork. A similar case, in which congestive failure resulted from auricular fibrillation when there was no evidence of organic heart disease, was reported by Brill.[9]

SUMMARY

Three cases of Wolff-Parkinson-White Syndrome are described (short P-R and long QRS intervals in patients who are prone to paroxysmal tachycardia, but have no apparent evidence of organic heart disease). Whereas in cases of this type as originally described there were paroxysms of auricular tachycardia or fibrillation, these three patients had paroxysms of ventricular tachycardia. In one case an erroneous diagnosis of acute coronary thrombosis, which it closely simulated, was made. In another case there was evidence of an acute cardiac emergency, and the patient responded promptly to quinidine therapy.

An additional case is described which shows that advanced congestive failure can result, even in the absence of organic heart disease, if a rapid heart rate is permitted to continue for a long time.

These patients present clinical problems that may be serious, and yet are amenable to the proper therapy.

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Department of Clinical Reports

SIGNIFICANCE OF GENERALIZED SYSTOLIC PULSATION OF VEINS, WITH REPORT OF A CASE IN WHICH THERE WAS MARKED PULSATION OF VARICOSE VEINS

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SYSTOLIC pulsation in the peripheral veins has been recognized for many years as a sign of tricuspid incompetency. Benson,[1] in 1836, made a comprehensive study of a case of venous pulsation in the upper extremities, and he appears to have been the first clinician to note that the phenomenon was related to failure of the right ventricle. One year later, King[2] compiled from the literature a series of cases of pulsating veins, and elaborated further on their cause. In his "Essay on the Safety Valve Function in the Right Ventricle of the Human Heart," he postulated that the inherent weakness of the tricuspid valve acted as a safety mechanism to relieve an overburdened right ventricle. That insufficiency of the tricuspid valve is a cause of pulsating veins is now generally accepted. Since King's communication, other excellent studies have been reported. Kerr and Warren[3] reported fifty-six cases in 1925, and very recently White and Cooke[4] submitted their observations in six cases.

Systolic pulsation of varicose veins has not been observed as commonly. Friedreich,[5] in 1867, in a review of the literature pertaining to venous pulsation in the extremities, cited Manly, Goubler, and Verneuil, who noted pulsation in the varicose veins of one leg. A few isolated reports have appeared since. Teufl,[6] in 1936, reported thirty-one cases of pulsating veins; eleven patients in this series showed pulsations of varicose veins in combination with pulsation of other veins. In eight cases the diagnosis was verified by autopsy; either organic or relative tricuspid insufficiency was present. Teufl first stressed the point that if the venous pulsations disappeared with the termination of right-sided heart failure, the lesion was relative tricuspid insufficiency. If, on the other hand, the pulsations persisted after signs of heart failure disappeared, the lesion was organic tricuspid insufficiency.

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We have recently had the opportunity to observe a woman, 46 years of age, who presented marked systolic pulsations of the veins of the neck, head, retinae, and upper extremities, pulsation of the liver, and, finally, marked pulsations of varicose veins of the lower extremities. Our purpose in this report is to call attention to the possible existence of some pathologic condition other than tricuspid insufficiency which may be a factor in producing pulsation of the peripheral veins.

REPORT OF CASE

Mrs. M. S., Case No. 631613, aged 41, a housewife and mother of six children, was first admitted to the University of Minnesota Hospital Oct. 13, 1934. Her chief complaints at that time were intermittent dyspnea on exertion, and edema of the ankles for the preceding seven years. During the three months prior to admission she had been forced to remain in bed because of progressive dyspnea, orthopnea, ascites, and edema. During the preceding five years she had had varicose veins of the lower extremities, and, for four months, a varicose ulcer on her right ankle. There was no rheumatic history. One living sister had "heart trouble." Her mother had died at 80 from heart disease. Her husband and all of her children were living and well except for one son who had questionable heart disease.

Physical examination on admission revealed a well-developed and well-nourished white woman who was moderately dyspneic and orthopneic. The superficial and deep jugular veins were distended and exhibited a systolic pulsation. Ophthalmoscopic examination revealed no abnormalities. A moderate, bilateral hydrothorax was present. The heart was somewhat enlarged, both to the left and right. A systolic thrill was felt at the apex. A loud systolic murmur was heard over the entire precordium, but was maximum over the apex. A presystolic murmur was present over the mitral area. The heart rate was rapid and the rhythm was normal except for a few extrasystoles. The blood pressure was 166/110 on admission. There were an enlarged, tender liver, moderate ascites, and moderate edema of the lower extremities. On the medial aspects of the legs there were pulsating varicose veins; the pulsations were more pronounced on the right, especially in two bulging areas, 2½ cm. in diameter, just below and above the medial aspect of the right knee. Proximal compression of the veins stopped the pulsation. The Trendelenburg test was positive. A varicose ulcer was present on the lateral aspect of the right ankle.

Urinalysis showed a specific gravity ranging from 1.010 to 1.027, and albumin from 0 to 1+. The hemoglobin was 94 per cent, and leucocyte count, 5,200, with 82 per cent neutrophiles and 18 per cent lymphocytes. The blood nonprotein nitrogen was 37.8 mg. per cent. The phenolsulphonephthalein test showed a 55 per cent excretion of the dye in two hours. On admission the vital capacity was 1300 c.c. The basal metabolic rate was +5 per cent. The electrocardiogram showed a prolonged P-R interval (0.22 sec.), sinus tachycardia, right axis deviation, a diphasic T_1 and T_2, and low potential in all leads. A teleroentgenogram showed that the total transverse diameter of the chest was 26.5 cm.; the M.L. was 10.0 cm., and the M.R., 7.6 cm. (total 17.6 cm.). Fluoroscopic examination showed that the heart was considerably enlarged, chiefly in the region of the right ventricle and right auricle. The conus pulmonalis was prominent, and there was slight enlargement in the region of the left ventricle.

The treatment consisted of strict bed rest, restriction of salt and fluids, diuretics, sedatives, and full digitalization. Her heart failure disappeared under this regime. However, because of frequent pulsus bigeminy and the onset of auricular fibrillation,

the digitalis was discontinued. The bigeminy persisted, so that digitalis was begun again, and, in addition, the patient was given quinidine, which restored normal rhythm. At the time of discharge, Dec. 16, 1934, the blood pressure was 120/80. The venous pressure was not taken. Unfortunately, no record was made at this time as to whether the pulsation of the veins persisted after the heart failure had been relieved.

The diagnosis at the time of discharge was rheumatic and hypertensive heart disease, marked cardiac enlargement, auricular fibrillation, congestive heart failure, mitral stenosis and regurgitation, relative tricuspid regurgitation, with pulsating veins, and varicose veins of the lower extremities, with a varicose ulcer of the right ankle.

The patient was next seen June 16, 1935, in the Outpatient Cardiac Clinic. She had taken no quinidine for three weeks, and during this period there were numerous extrasystoles. The heart rate was 114 per minute, and auricular fibrillation was present. An orthodiagram showed relatively the same cardiac measurements as on her previous admission.

Her second admission was July 7, 1935. Prior to this the patient had been bedridden for three months because of an upper respiratory infection, characterized by a persistent, hacking cough, weakness, and generalized pain, all of which accentuated her cardiac symptoms. No digitalis had been taken during this period.

Physical examination revealed the same abnormalities as on the previous admission, except that there were increased pulsations of the veins of the neck and the varicose veins of the legs. Bilateral hydrothorax was present. The blood pressure was 140/80, and she had auricular fibrillation, with a ventricular rate of 120. The liver was enlarged, and marked edema of the lower extremities was noted.

The laboratory findings were essentially unchanged. The electrocardiogram showed low amplitude of the QRS complexes and auricular fibrillation. The patient was redigitalized, recovered from her heart failure, and was discharged Sept. 11, 1935.

The third admission was on March 3, 1939. Beginning in September, 1938, heart failure had developed gradually, and three weeks prior to admission had become very marked after an upper respiratory infection.

Physical examination revealed a poorly nourished, cyanotic, dyspneic, and orthopneic woman. The superficial veins were distended, and systolic pulsations were noted, especially in the temporal, jugular, basilic, external mammillary, crural, and varicose veins of the lower extremities. Ophthalmoscopic examination showed a small patch of retinal atrophy in the right eye and pulsating retinal veins. There was a right-sided hydrothorax, and moist râles were present throughout both lungs. On percussion, the cardiac outline appeared to be larger than before. Systolic and diastolic thrills and murmurs were found over the apical area. The systolic murmur was heard over the entire precordium. The blood pressure was 134/92. Auricular fibrillation was present. The edge of the liver was tender, and could be palpated four fingerbreadths below the right costal margin. Systolic pulsations were seen on inspection and also felt on palpation. Pressure over the liver region accentuated the distention of the jugular veins. Marked ascites and edema of the lower extremities were present. Proximal compression of the superficial saphenous and basilic veins obliterated the distal pulsation of the veins.

The significant laboratory data were as follows: Blood nonprotein nitrogen, 33.6 mg. per cent; total plasma protein, 7.2 Gm., with 3.4 Gm. of albumin and 3.3 Gm. of globulin; cholesterol, 152 mg. per cent; icterus index, 7. Repeated blood cultures were negative. The phenolsulphonephthalein test showed 58 per cent excretion at the end of two hours. The vital capacity was 1100 c.c. Venous pressure measurements were as follows: right antecubital vein, 27 cm. of saline, which, with right upper quadrant pressure, rose to over 40 cm.; left antecubital

vein, 27 cm.; right femoral vein, 34.5 cm.; and left femoral vein, 33.5 cm. The circulation times were definitely prolonged, i.e., arm-to-tongue (decholin), 28 sec.; arm-to-lung, 13 sec. (ether), and lung-to-tongue, 15 sec.

The electrocardiogram showed bigeminy, numerous premature contractions from various foci, and auricular fibrillation. Roentgenograms of the lungs and heart revealed pleural effusion on the right, pulmonary congestion, and massive cardiac enlargement, with a bulge in the region of the conus pulmonalis. Roentgenograms of the tibia and fibula showed no periostitis.

The right pleural sac was tapped. Diuretics, sedatives, and digitalis were given. Thiamin chloride produced no beneficial effect. The venous pressure went as low as 20 cm. of saline in the antecubital veins. The patient gradually improved clinically. Digitalis was discontinued for a time because of toxic signs, both clinical and electrocardiographic, but was begun again later.

A cardiac psychosis developed April 4, 1939. Digitalis was promptly discontinued, and hypertonic glucose solution was given intravenously daily. The icterus index rose to 15, and the van den Bergh reaction became diphasic. On April 26, 1939, the patient was taken home by her husband, against advice.

The diagnosis, in addition to her cardiac condition, was somatic psychosis due to cardiac disease, and icterus due to chronic passive congestion of the liver.

The fourth admission to the hospital was on June 6, 1939. She had taken no digitalis since her previous discharge, and was suffering from severe cardiac failure. The physical signs were essentially the same as on the previous admission. There was marked cyanosis, and auricular fibrillation with a ventricular rate of 140 was present. The blood pressure was 120/70. The total plasma protein was 6.2 Gm., with 2.9 Gm. of albumin and 3.3 Gm. of globulin. The venous pressure was 32 cm. The column of saline in the manometer of the venous pressure apparatus pulsated synchronously with the venous pulsations, and the range of pulsation between systole and diastole was 1 cm. This was the greatest fluctuation of pressure observed at any time. The electrocardiogram and roentgenograms of the chest were unchanged. Repeated blood cultures were negative. On June 7, 1939, the blood nonprotein nitrogen was 54.6 mg. per cent, and the icterus index, 23, with a delayed van den Bergh reaction. The 24-hour urine urobilinogen excretion was 274 mg., indicating severe liver damage.[7]

The treatment, on admission, consisted of paracentesis, oxygen, sedatives, and digitalis. Because of the cardiac psychosis, she was transferred to the psychiatric ward. The venous pressure declined to 17.5 cm. of blood on July 11, 1939, but the pulsation of the veins did not decrease. The patient was again discharged against advice on Aug. 18, 1939.

The fifth admission was on Aug. 28, 1939. Both the cardiac psychosis and cardiac failure were marked. There was infranuclear paresis of the left seventh and twelfth cranial nerves. The venous pressure was 19 cm. of blood, and there was marked pulsatory activity of the veins.

Digitalis and supportive cardiac therapy were begun again. On Aug. 30, 1939, the patient had a cerebral embolus, from the effects of which she recovered uneventfully and rapidly. In addition, both her neurologic and cardiac status improved. The patient was transferred Sept. 14, 1939, to the state hospital, where she died on Dec. 17, 1939.

In résumé, the history dated back twelve years, at which time dyspnea first appeared. Thereafter the clinical picture was one of recurrent and progressive attacks of right- and left-sided cardiac failure. For five years the outstanding clinical feature was tricuspid insufficiency, characterized by increased venous pressure, pulsating liver, and generalized systolic pulsations of the veins, including the varicose veins. Severe cardiac failure and a psychosis were present during the last six months of the patient's life.

The patient died Dec. 17, 1939, at the Fergus Falls State Hospital. Eight hours after death a post-mortem examination was done.* The important abnormalities were as follows: The abdomen was distended and the lower extremities were edematous (about four plus). The peritoneal cavity contained 8000 c.c. of clear, amber fluid. Each pleural cavity contained one liter, and the pericardial cavity, 30 c.c., of a similar transudate. The heart was sent to us for examination. Both lungs were heavy and edematous. The liver had the typical nutmeg appearance. The gall bladder contained gravel-like stones. No arteriovenous aneurysm was found. The brain was not examined.

Examination of the heart† revealed the following: It weighed 395.5 grams after the intrapericardial vessels had been removed and the endocardial surfaces cleaned of blood. Preliminary examination disclosed very slight dilatation of the left atrium and marked dilatation and hypertrophy of the right atrium and right ventricle. The mitral valve was thickened and partly calcified, and the chordae tendineae were shortened and thickened. The lumen was slit-like, and measured 1.2 cm. in length and 0.4 cm. in width, so that there were obviously both mitral regurgitation and stenosis of severe degree. No vegetations were present. The other valves showed nothing of note.

The two atria, with their epicardial tissues, weighed 114 grams. The left atrial muscle appeared normal; the circumference was 20 cm., and the height, 5 cm. The right atrial muscle was markedly hypertrophied; the circumference was 18 cm., but the height was 12 cm.

The epicardial tissues over the ventricles weighed 16 grams—9 grams over the right ventricle and 7 grams over the left. The coronary arteries appeared normal.

The ventricular muscle weighed 265.5 grams. The right ventricle weighed 153.3 grams, and the thickness of its free wall varied from 0.3 cm. at the base to 0.2 cm. near the apex; the left ventricle weighed 112.2 grams, and the thickness of its wall varied from 1.8 cm. to 0.6 cm. The relative weight of the right to the left ventricle was 1.4:1.

The pulmonary conus was elongated; it measured 5.4 cm., and its width was increased to 11.0 cm. The ostium of the tricuspid valve was 11.9 cm., and that of the pulmonary valve, 8.4 cm. The mitral ostium was 5.2 cm., and the aortic, 6.6 cm. The inflow tract of the right ventricle measured 6.8 cm., and the outflow tract, 10.4 cm. On the left side the inflow tract was 6.9 cm., and the outflow tract, 7.7 cm.

DISCUSSION

During the clinical observation of this patient we were inclined toward a diagnosis of organic tricuspid insufficiency, rather than relative tricuspid insufficiency. Our only reason was the fact that the pulsations persisted after the venous pressure fell. This was not conclusive evidence, however, for the venous pressure never did return to normal limits. At necropsy the tricuspid leaflets appeared normal, but of much more interest was the fact that the tricuspid orifice was only slightly, but sufficiently, dilated to give rise to relative tricuspid insufficiency. We have noted the condition of the tricuspid ring in numerous cases of congestive failure in which the degree of stretching was as much or

*We are indebted to Dr. Stanley Lindley and Dr. R. Reader, of the Fergus Falls State Hospital, who did the autopsy and kindly sent us the heart for further examination.

†We are indebted to Dr. B. J. Clawson, of the Department of Pathology, who made the gross examination of the heart, and to Dr. George Higgins, pathologist at the Glen Lake Sanatorium, who dissected the heart chambers and made careful measurements of the cardiac structures.

greater than in this case, yet no pulsation of the veins was present during life.

It would thus seem highly improbable that the marked venous pulsations in this case are to be explained as a result of the tricuspid insufficiency alone.

Another outstanding feature of this case was the minimal dilatation of the left atrium, in spite of the severe grade of mitral stenosis. This suggested that there was some impediment to the volume flow of blood through the pulmonary circuit.

From a consideration of these points, it would appear that some other condition was responsible, in part, for the marked pulsation of the veins. This could be explained best by some factor which would set up resistance to the flow of blood through the lesser circulation. The most obvious explanation would appear to be narrowing of the pulmonary vascular bed. It is well recognized that secondary arteriosclerotic changes may occur in the pulmonary vessels in long-standing cases of mitral stenosis. An abundance of evidence is found in the literature to support this view.[8-13] At times the pulmonary sclerosis may be marked, with involvement of the large, medium-sized, and small vessels, which results in narrowing of the vascular bed. This is especially true when a "button-hole" mitral stenosis exists.[14] The effect of these changes would be to increase greatly the right intraventricular pressure. With the inception of relative tricuspid insufficiency, the release of the pulse wave into the venous system is made possible by a vigorously contracting right ventricle. Although proof of pulmonary artery narrowing is lacking in this case because the lungs were not available for study, it is reasonable to assume that such a condition could exist, and that this, in addition to relative tricuspid insufficiency, could very well explain the marked retrograde transmission of the pulse wave from the right ventricle. Careful anatomic examination of the pulmonary vascular tree should be made in all cases of tricuspid insufficiency in which pulsation of veins was present during life.

CONCLUSIONS

1. A case of marked, generalized, systolic pulsation of veins is presented. Striking pulsations of the varicose veins in the lower extremities were an outstanding feature.

2. This study suggests that a pulmonary factor may play an important role in the mechanism which is responsible for systolic pulsation of peripheral veins.

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LEUCEMIC PERICARDITIS

Report of a Case of Lymphatic Leucemia in Which Massive Pericardial Effusion Was the Earliest and Most Outstanding Manifestation

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Philadelphia, Pa.

INTRODUCTION

INVOLVEMENT of the heart by infiltration into the pericardium and myocardium by retrograde extension from adjacent diseased lymph nodes has already been described in cases of lymphosarcoma[1, 2] and tuberculosis.[3] Although similar involvement of the heart can occur in lymphatic leucemia,[4] we are not aware of a reported instance in which a massive pericardial effusion secondary to leucemic infiltration of the pericardium constituted the first clinical manifestation of the leucemic state. We therefore wish to report the following case of leucemic pericarditis, not only because of its rarity, but because it simulated in many ways the so-called "clinically primary" tuberculous pericarditis, and therefore serves to emphasize certain criteria which should be fulfilled before the diagnosis of the latter condition can be made with certainty.

CASE REPORT

M. McG., a colored girl, 15 years of age, was originally admitted to the Frederick Douglass Memorial Hospital on the medical service of Dr. Truitt and Dr. Greene on September 17, 1937. Several weeks before admission she had developed an unproductive cough and weakness, followed by a progressive weight loss, anorexia, dyspnea on very slight exertion, and fever. The outstanding features of the physical examination were as follows: the patient was undernourished, breathless (respiratory rate, 36), febrile (temperature 102° F.), and obviously acutely ill. The veins of the neck were engorged in both the sitting and supine positions. No cervical lymph nodes were palpable. There was diffuse enlargement of the cardiac area both to the right and left, with widening of the area of supracardiac dullness. The latter was more marked in the supine than in the upright position. The apex beat was not palpable and the heart sounds were muffled. The rhythm was normal, and no murmurs or pericardial friction rub were audible. The blood pressure was normal (110/80). A rather marked parodoxical pulse was present. The abdomen and extremities were essentially negative except for a moderate degree of wasting. Under the fluoroscope, the cardiac shadow was seen to be considerably enlarged, but no cardiac contractions were visible. In addition, it was noted that the supracardiac shadow was widened and that the mediastinal lymph nodes were enlarged. The electrocardiogram showed deeply inverted T waves in all the limb leads. The blood cell count was normal except for a slight secondary anemia. The leucocytes numbered 7,500, and the differential count was normal. On the basis of the history, physical signs, and laboratory data, a diag-

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nosis of tuberculous pericardial effusion was made. On September 18, 1937, the first pericardial paracentesis was performed. This yielded 500 c.c. of amber-colored, slightly cloudy fluid. A corresponding amount of air was injected. A second fluoroscopic study, after the establishment of the pneumopericardium, clearly showed the widened supracardiac shadow, the enlarged hilar lymph nodes, the thickened pericardium, and the small heart. Although this combination of signs has been considered characteristic of tuberculous pericarditis, examination of a smear made from the pericardial fluid failed to reveal any tubercle bacilli. A guinea pig was therefore inoculated with the fluid on the same day.

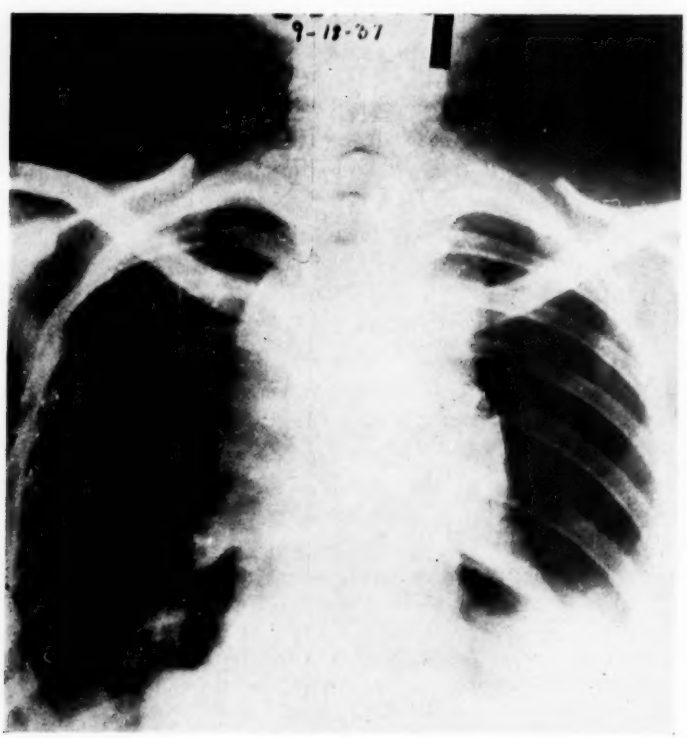

Fig. 1.—Roentgenogram after pneumopericardium. Note the enlarged mediastinal nodes, widened supracardiac shadow, thickened pericardial sac, and small heart.

On September 27, 1937, a second pericardial paracentesis was performed; a total of 700 c.c. of fluid, now serohemorrhagic in character, was removed, and a corresponding amount of air injected. The roentgenogram which was taken after this procedure is shown in Fig. 1. In smears made from this fluid it was again impossible to demonstrate the presence of tubercle bacilli, and a second guinea pig was therefore inoculated. The patient subsequently developed a left-sided pleural effusion which was tapped by Dr. Greene on September 30, 1937, and 950 c.c. of serosanguineous fluid were removed. This was stained and examined for tubercle bacilli, with negative results. Subsequently, the patient had fever of an intermittent type, and repeated reaccumulations of fluid in the left side of the chest; the latter was tapped at frequent intervals. Physical examination, fluoroscopic study, and roentgenograms of the chest failed to reveal any evidence of a reaccumulation of fluid in the pericardial cavity. On November 11, 1937, the guinea pigs were sacrificed and examined. No evidence of tuberculosis was found.

On November 12, 1937, the patient left the hospital with a final diagnosis of pericarditis and pleurisy with effusion, probably tuberculous in origin. After remaining at home for four days, she was admitted to the medical service of Dr. David Riesman at the Philadelphia General Hospital on November 16, 1937. Physical examination at this time revealed that the patient had obviously lost more weight, although she did not appear to be acutely ill. A fever of 102° F. was present. Lymph nodes were easily palpable in the neck, both axillae, and

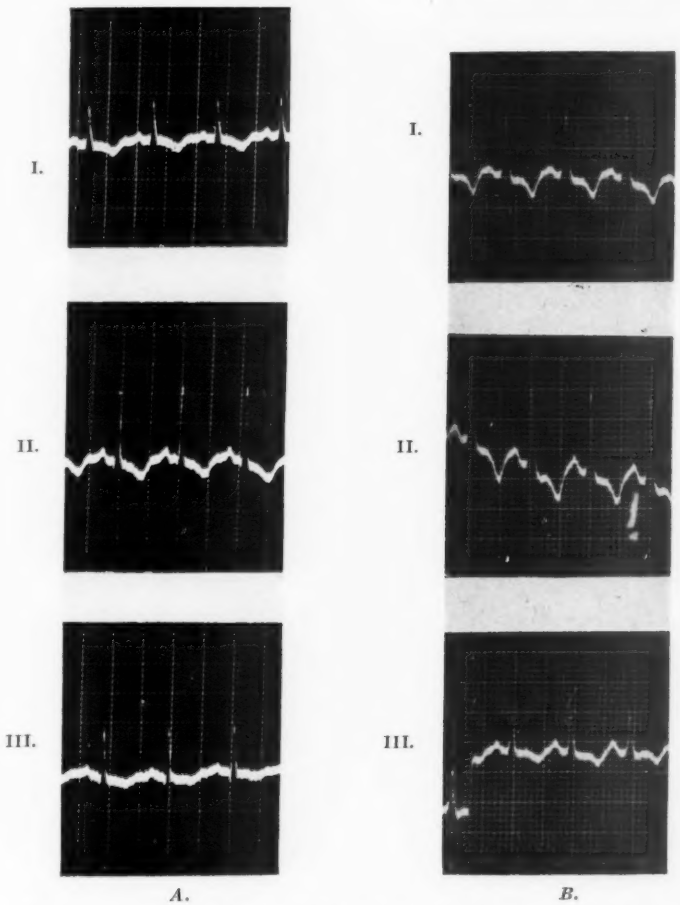

Fig. 2.—Electrocardiograms taken—*A*, While there was a large effusion. *B*, When there was no effusion. Note inverted T waves in all the limb leads, and that there is no material difference between the two tracings.

in the inguinal regions. Signs of fluid in the left side of the chest, with displacement of the heart to the right, were readily evident. The heart presented nothing remarkable except for simple tachycardia and a widened area of supracardiac dullness. The edge of the liver was felt at the level of the umbilicus, and the edge of the spleen was palpable on deep inspiration. The sternum was very sensitive to palpation and percussion. The electrocardiagram was similar to the one taken at the Douglass Hospital; it showed inverted T waves in all the limb leads (Fig. 2). Roentgenograms of the chest revealed a large pleural effusion on the left side, with displacement of the normal-sized heart and mediastinum to the

right. The following day, another roentgenogram, taken after the removal of 700 c.c. of pleural fluid, showed that the base of the heart and upper mediastinum were considerably widened as a result of enlarged lymph nodes. A diagnosis of "tuberculous mediastinal adenitis, or some form of lymphoblastoma" was made by the roentgenologist. The leucocytes, the day after admission, numbered 116,000, of which 97 per cent were lymphocytes. Two days later the leucocyte count had risen to 191,000, all of which were lymphocytes. A biopsy of one of the inguinal nodes revealed histologic changes typical of lymphatic leucemia. Before any further studies could be carried out, the patient died suddenly and unexpectedly on November 25, 1937.

Fig. 3.—Section through myocardium. Note leucemic infiltration extending into myocardium, through its lymphatics (×92).

An autopsy was performed by Dr. Harold Johnson on the same day, and the following notes were made: "After the chest was opened, the mediastinum was seen to be considerably widened as a result of infiltration of gray-white tissue in which lymph node outlines could be vaguely recognized. This infiltration extended down over the parietal pericardium. The parietal pericardium was loosely adherent to the visceral pericardium, because of an infiltration of similar tissue into the visceral pericardium. This was rough and shaggy, in areas. There was no excessive amount of fluid in the pericardium. The heart was of normal size and weighed 330 grams. The myocardium was a pale pink in color, and through this there was a heavy mottling of gray-white areas. The heart was otherwise normal. The left lung was collapsed, and its pleural surface was irregularly thickened with opaque nodules. Within the left pleural cavity there were 800 c.c. of serosanguineous fluid. The right lung was normal. The spleen weighed 120 grams, its parenchyma was soft, its cut surface was pale red, and it was peppered with gray-white spots throughout. The left kidney showed a few bulging, red,

speckled nodules on its surface. The bone marrow from the vertebrae and the femur was grayish red and soft. The lymph nodes along the aorta, in the mediastinum, mesentery, and subcutaneous regions were all enlarged, firm, and gray-white in color.'' The diagnosis from these gross abnormalities was as follows:

1. Leucemic infiltration into the pericardium, myocardium, left pleura, spleen, liver, kidney, lymph nodes, and mediastinum.
2. Hyperplasia of the bone marrow.

Gross examination of the brain by the neuropathologist, Dr. Helena Riggs, showed chronic passive congestion. Histologic examination of sections from various organs confirmed the gross diagnosis. The infiltration into the myocardium is seen in Fig. 3.

DISCUSSION

A large leucemic pericardial effusion, such as was encountered in this case, does not present itself often. From the point of view of frequency, therefore, the lesion is not a very important one. When it does occur, its diagnosis will probably not be as difficult as it was in this instance. Its recognition will depend, first, upon the diagnosis of the pericardial effusion, and, second, on discovery of the leucemic state. The mistake here occurred because the leucemia, early in the course of the disease, was unaccompanied by the usual leucocytosis, hemorrhagic tendencies, and lymph node enlargement. However, the purpose of this report is not to emphasize the difficulties in the diagnosis of leucemic pericardial effusion, but rather to show that, because of the insidious onset of the illness, the fever without a corresponding leucocytosis, the massive serosanguineous pericardial effusion, the small heart, the absence of cardiac murmurs, the T-wave changes in the electrocardiogram, and the supposedly associated tuberculosis, as represented by the enlarged mediastinal lymph nodes, there was in this case a group of abnormalities which are recognized as characteristic of tuberculous pericarditis.[5, 7-10] However, the failure to demonstrate the tubercle bacillus in the pericardial fluid proved to be significant in this instance. The conclusion is therefore warranted, from this experience, that reservations should be placed upon the diagnosis of tuberculous pericarditis when the causative organism cannot be recovered from the pericardial effusion, even though some observers[9] consider that associated mediastinal disease is of equal etiologic significance.

SUMMARY

1. A case of lymphatic leucemia is reported, in which a massive pericardial effusion, simulating the tuberculous variety, was the only striking abnormality early in the course of the disease.

2. The difficulty in making the correct diagnosis during the aleucemic stage is discussed.

3. The subsequent development of enlarged lymph nodes and the characteristic leucocytosis enabled a correct diagnosis to be made before death, and this was confirmed by necropsy.

4. Emphasis is placed upon the necessity of demonstrating the tubercle bacillus in the pericardial fluid, whenever a diagnosis of tuberculous pericarditis is entertained.

We wish to thank Dr. David Riesman for permission to report this case, and to acknowledge the cooperation of the Division of Pathology in the preparation of the report.

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Department of Reviews and Abstracts

Selected Abstracts

Hill, W. H. P., and Andrus, E. C.: The Cardiac Factor in the "Pressor" Effects of Renin and Angiotonin. J. Experimental Med. **74**: 91, 1941.

Upon the isolated hearts of cats perfused with Ringer-Locke solution, renin produced no significant effect. Angiotonin, on the other hand, brought about decrease in coronary flow and increase in amplitude of beat without any consistent effect upon heart rate.

Both renin and angiotonin augmented the cardiac output and raised the "arterial" pressure in the Starling heart-lung preparation; here too without influence on the heart rate.

Electrocardiograms recorded before, during and after the pressor effects of renin and angiotonin in the anesthetized cat showed no abnormalities until the blood pressure had risen above 190 mm. Hg when various types of cardiac arrhythmias appeared. These were prevented, or normal rhythm was restored, by cutting the vagus nerves or injecting atropine.

It is concluded that the "pressor" effects of renal pressor substances include direct stimulation of the myocardium and augmentation of ventricular beat. Unless these actions lead to excessive decrease in diastolic volume of the ventricles, the cardiac output will be increased. The significance of this in the production of the pressor effect is discussed.

AUTHORS.

Strombeck, J. P.: Effects of Arterial Resection. Experimental Angiographic Study. Acta chir. Scandinav. **83**: 510, 1940.

The animal experiments carried out by Leriche's co-workers, Fontaine and Schnatter, with the view to showing the mode of action of arterial resections, have been checked by using a technique more free from objections. Resections of thrombotic portions of arteries showed no reliable effect as demonstrated by arteriograms.

AUTHOR.

Karsner, H. T., Simon, M. A., and Fujiwara, T. F.: Relation of Experimental Pulmonary Arterial Hypertension to Arteriosclerosis. Arch. Path. **31**: 585, 1941.

What is probably a slight degree of pulmonary arterial hypertension, lasting over many months, is induced by the lodgment of large numbers of small seeds in the small arteries and arterioles of the lungs of the dog. The evidence of such hypertension is found in the squaring of the ends and the increase of the transverse diameters of the nuclei of the cardiac muscle. The probable slight increase of pressure, persistent and prolonged, does not cause pulmonary arteriosclerosis.

AUTHORS.

Feldt, R. H., and Wenstrand, D. E. W.: The Cold Pressor and the Breath-Holding Test. An Analysis of Results in Two Hundred Subjects. Arch. Int. Med. 67: 1157, 1941.

In the present series of 200 cases the mean responses of the blood pressure to the cold pressor test and the breath-holding test were similar except that breath holding obtained a slightly greater systolic reaction among normal hyporeactors. In most of our subjects the response to the cold pressor test was the same as or higher than the response to the breath-holding test. Wide differences between the reaction to the cold pressor test and the reaction to the breath-holding test were at times found in the same person. Hyperreaction to cold was found in thirty-nine subjects who were hyporeactors to breath holding. Hyperreaction to breath holding was found in sixteen subjects who were hyporeactors to cold.

AUTHORS.

Scuderi, Carlo S.: Fat Embolism: A Clinical and Experimental Study. Surg., Gynec. and Obst. 72: 732, 1941.

After injury to bone marrow fat or adipose tissue, there is a disintegration of the supporting fibrous tissue with liberation of fat. Naturally there are ruptured blood vessels in the vicinity of the injury. The arteries squirt more blood into the area, thereby increasing the pressure, while the veins remain open and absorb the fatty mixture by venous suction. Fat embolism is more common in fracture than in any other condition because the veins are encased in a bony wall and hence cannot collapse as elsewhere in the body; thus they remain wide open for the admittance of the fatty mixture. Death from fat embolism is not common after fractures. Grondahl states that the occurrence is fatal in only 1 out of 300,000 fractures.

There is no clinical correspondence between the apparent injury and the degree of resulting lipemia. Injuries which are apparently identical may in one individual be followed by a fatal lipemia, while in another the same injuries may cause but a slight disturbance. The onset may be sudden, within a few hours of the injury, but usually does not become manifest until the third or fourth day. Once the symptoms set in, they may vary from a slight irritability and excitability to maniacal periods associated with high grade delirium and death. In the more severe cases dyspnea appears with gradual passive congestion of the lungs as more capillaries are obstructed. A cough of productive nature may appear and lead to a diagnosis of bronchopneumonia.

The majority of cases of fat embolism are so mild that they do not cause symptoms, or so severe that death results in a few days from involvement of the lungs or the brain. During life the diagnosis is justified only if there is a history of an injury, with the typical clinical manifestations. Confirmatory signs are the presence of fat in the urine, the demonstration of fat emboli in the retinal vessels, and the appearance of petechial hemorrhages in the chest, shoulders, and neck.

The prognosis in fat embolism should always be reserved because some of the patients who appear to be coming along well suddenly grow worse and die. Most of the patients recover, but due to the fact that only the fatal or very sick cases are diagnosed and the mild cases overlooked, most people have the reverse idea.

Since all the bone marrow fat extracted from a femur is not sufficient to cause death, the author believes, from experimental evidence, that oleic acid, one of the split products of the neutral olein of bone marrow, is the probable etiologic agent. This substance is seven times as lethal as neutral bone marrow fat and sufficient quantity could easily be available.

M. NAIDE.

Cooke, W. T., and White, P. D.: Auricular Fibrillation Following the Injection of Acetyl-B-Methyl Choline Chloride (Mecholyl) During an Attack of Paroxysmal Auricular Tachycardia or Flutter. Cardiologia 4: 313, 1940.

In a new case of paroxysms of tachycardia with an electrocardiogram showing short P-R intervals and wide QRS complexes and otherwise normal heart (type described by Wolff, Parkinson, and White), auricular fibrillation of one and one-half hours' duration was produced during an attack of paroxysmal auricular tachycardia (or flutter) by an injection of acetyl-B-methylcholine chloride (5 mg.).

AUTHORS.

Kisch, B.: The Changes of the Chest-Leads of the Electrocardiogram Due to Damage of the Heart's Surface. Cardiologia 4: 318, 1940.

A small damage concerning the contractility of the surface layer of the heart muscle produced experimentally by local KCL application is sufficient to change the chest lead electrocardiogram in a high degree, even if the standard electrocardiogram leads show no remarkable changes.

In a right side damage the right chest lead is more changed than the left chest lead and vice versa.

If the damage is strictly limited to one side of the ventricle, there is a lifting of S, the S-T segment and T in the homolateral chest lead and a depression of the same parts of the electrocardiogram in the heterolateral chest lead.

Should both parts of the ventricle be damaged, mixed effects result which depend on the place and the size of the damage.

Experiments on the frog's heart, which has only one ventricle, proved, that also in our other animal experiments the changes produced in the chest lead are not to be referred to changes in the behavior of the right or left chamber in an anatomic sense, but only to a change in the behavior of the right or left part of the surface layer of the heart muscle.

These experiments show clearly the importance of taking at least a right and a left chest lead in all cases of clinical investigations, for arriving at more exact diagnosis.

AUTHOR.

Teran, V. S.: Three Observations on Complete Intermittent Auriculo-Ventricular Block. Rev. argent. de cardiol. 7: 374, 1941.

Three observations of intermittent complete heart block are reported, one of them with a manifest vagal factor in its production.

A curious form of auricular arrhythmia was observed in the course of ventricular arrest in one of the observations.

The ventricular complexes during complete block showed as compared with those during sinus rhythm; increase in amplitude and duration of QRS, longer duration of ST, and increase in size of the T wave.

AUTHOR.

Cohen, L., Gray, I., Nash, P. I., and Fink, H.: Calcareous Aortic Stenosis: Report of Nine Cases With Autopsy Findings. Ann. Int. Med. 13: 2091, 1940.

Calcareous aortic stenosis is a disease predominantly affecting males and usually occurring past middle life, but occasionally encountered in younger persons. The outstanding physical signs are the typical murmur, accompanied by a diminished second aortic sound and a palpable thrill over the aortic area. The heart is enlarged. The stenotic aortic lesion is usually accompanied by changes (atheromatous) in the

aorta and coronary arteries and at times by calcific changes in the mitral valve and ring. The syndrome of angina pectoris and disturbances in cardiac rhythm are commonly seen in this disease. The occurrence of sudden death is a striking and frequent characteristic.

In this communication nine cases of calcareous aortic stenosis have been reported and the etiologic factors, morphologic changes, and clinical features have been discussed.

AUTHORS.

Bain, C. W. C., and Wray, S.: Ruptured Aortic Valve With Mycotic Aneurysm Due to Acute Bacterial Endocarditis. Brit. Heart J. 3: 132, 1941.

A case of rupture of the aortic valve with a mycotic aneurysm due to bacterial endocarditis has been described. The temperature was subnormal throughout the illness. Death took place quickly with signs of left ventricular failure.

AUTHORS.

Denenholz, E., and Rambar, A. C.: Rheumatic Fever in a Newborn Infant. Am. J. Dis. Child. 61: 1044, 1941.

A case of probable rheumatic fever in a breast-fed infant, 10 days old, is reported.

Stone, S.: Treatment of Sydenham's Chorea by Fever and Vitamin B Therapy. New England J. Med. 223: 489, 1940.

Twenty patients with severe, moderately severe, and mild cases of Sydenham's chorea were treated. Five of the seven cases received artificial fever therapy, together with vitamin B complex given orally and thiamin chloride given parenterally. One severe and one moderately severe case received thiamin chloride parenterally and vitamin B complex orally, while all the others received oral medication only.

In the electropyrexia-treated cases recovery was produced with about fourteen hours of fever at 104° F. or over. When this was combined with vitamin B therapy, advanced cardiac conditions were found to be no contraindication to the fever treatment. Usually a change for the better in the carditis was noted at the end of the treatment.

One of the two cases treated with thiamin chloride responded with cessation of symptoms after the second intravenous injection of 10 mg. of the drug.

Various degrees of behavior disturbances were seen in most of the moderately severe and milder cases. They all received 4 to 8 c.c. of vitamin B complex orally, three times daily. The improvement in physical manifestations was less rapid than it was in the fever-treated cases, but most of the symptoms disappeared within one month. No hospitalization was required for any patients in this group. Improvement was noted in their behavior concomitantly with the change for the better in the choreic manifestations.

AUTHOR.

Landis, E. M.: Hypertension and the Pressor Activity of Heated Extracts of Human Kidneys. Am. J. Med. Sc. 202: 14, 1941.

Heated kidney extracts were prepared from tissue obtained at autopsies of sixteen cases with normal blood pressure during life and of thirty-four cases with marked hypertension. Anesthetized, nephrectomized rabbits were used for assay. Kidney extracts prepared from cases of benign hypertension and chronic glomerulonephritis were not more active than those of normal kidneys. The four extracts which showed pressor activity outside the normal range all came from cases of malignant nephro-

sclerosis. Nevertheless, the variations in activity, even in this group, make it impossible to demonstrate by these methods any clear relation between blood pressure during life and the renin content of kidney tissue after death.

The rise in blood pressure produced by active extracts of human kidneys is similar to that observed with renin from other species in that the blood pressure of the unanesthetized rabbit rises without a decrease of peripheral blood flow.

AUTHOR.

Cameron, D. E., and Rosen, S. R.: The Reactivity of Intracranial Vessels in the Aged. Am. J. M. Sc. **201**: 871, 1941.

A method is reported for investigating the reactivity of the cerebral vessels by observation of the spinal fluid pressure changes after intravenous injections of histamine.

A series of thirty-eight senile and fifty-five psychiatric patients at younger age levels was examined.

The average rise in spinal fluid pressure in the senile group was 34 mm. of water; the average for twenty-nine alcoholics included in the younger group was 86 mm. of water, and the rise for the twenty-six remaining patients in the younger group was 70 mm. of water.

The bearing which this may have on possible cerebral anoxemia in the aged was considered.

AUTHORS.

Montgomery, L. C.: A Case of Multiple Arterial Thrombosis Occurring in a Professional Blood Donor. Canadian M. A. J. **44**: 289, 1941.

A case is reported of a man, aged 44 years, a professional donor for three years, who developed a hemiplegia following the giving of a transfusion of 500 c.c. of blood. He had given 375 c.c. five days previously. Fifteen days after the hemiplegia he developed thrombosis of the splenic artery and while still in the hospital mesenteric thrombosis occurred. The latter two arterial thromboses were confirmed at operation and autopsy. The author suggests limiting the number of transfusions which a professional blood donor may give within a specified time. No prothrombin time was done on this patient.

M. NAIDE.

von Hofer, H.: The Influence of Gas-Mask Breathing on the Circulation of Men. Cardiologia **4**: 331, 1940.

The influence of the gas mask on the circulation, especially on the electrocardiogram, was tried in fifty persons. Changes were found in respiration, pulse rate, blood pressure and electrocardiogram. They were fairly the same as after mild exercise.

Conclusions were drawn that the gas-mask breathing is well endured by normals, but in cardiacs some damage must be assumed.

AUTHOR.

Veal, J. Ross, and Hussey, Hugh Hudson: The Venous Circulation in the Lower Extremities During Pregnancy. Surg., Gynec. and Obst. **72**: 841, 1941.

The assumption that postural dependent edema and varicose veins of the lower extremities in pregnant women are due to localized obstruction of the deep veins is supported by the types of pressure curve obtained when popliteal venous pressures are recorded during exercise.

The factors responsible for increasing the degree of localized venous obstruction in some pregnant women to the extent of causing edema or varicose veins or both are not perfectly understood. The size and position of the uterus are factors of recognized importance.

In pregnant women manifesting significant obstruction of the femoro-iliac veins, provision of adequate support for the superficial veins by means of elastic stockings minimizes or prevents the development of varicose veins.

AUTHORS.

Glaser, S. Thomas, and Lesser, Albert: Femoral Vein Ligation for Chronic Occlusive Arterial Disease. Am. J. Surg. **52**: 100, 1941.

Twenty cases of occlusive arterial disease of the lower extremities in which femoral vein ligation was performed have been presented and studied with follow-up for periods ranging up to two years. Definite relief of pain has been effected by this procedure in the majority of cases studied. Local demarcation and spontaneous separation of gangrenous tissue has been facilitated by femoral vein ligation in at least ten out of seventeen cases of gangrene.

The opening up of new collateral vessels is believed to have been produced and was satisfactorily demonstrated in at least two cases. Restoration of pulsation of the femoral artery was demonstrated in two cases after femoral vein ligation. There were no harmful or untoward effects as a result of the venous stasis produced. Femoral vein ligation is a simple procedure, easily performed under local anesthesia and unattended by any morbidity or mortality.

We believe this procedure to be of definite value in impending or early minimal gangrene of the lower extremities in the chronic occlusive arterial diseases.

AUTHORS.

Mulholland, John H., and Rovenstine, E. A.: Surgery in the Carotid Sinus Syndrome. Surgery **9**: 751, 1941.

The procedures employed in the diagnosis, preoperative care, anesthetic management, and operation in the carotid sinus syndrome are described. Mention is made of the clinical application of knowledge of this reflex area. Five cases are cited briefly. The symptoms of hyperactive carotid sinus reflex may be relieved by surgical denervation of the sinus.

AUTHORS.

Gray, Howard K., and Skinner, Ira C.: Constrictive Occlusion of the Superior Vena Cava. Surg., Gynec. and Obst. **72**: 923, 1941.

Three cases of constrictive occlusion of the superior vena cava in which the patients were treated by operation have been reported. In two of these there was probably an associated thrombosis, in the other the constriction was caused by a mass of calcified tuberculous glands. Mediastinotomy with the release of the constrictive bands seems indicated in those cases of superior vena caval obstruction in which the venous pressures are increasing and in which the symptoms are progressing.

AUTHORS.

Evans, W., and Paxon, T.: A Comparison of the Mercurial Diuretics Used in Heart Failure. Brit. Heart J. **3**: 112, 1941.

Certain mercurial diuretics were submitted to a clinical trial in fifty patients with heart failure, for the purpose of deciding their relative diuretic potency. The

best method of administering them was also investigated, as well as the best means of augmenting their natural diuretic action. Esidrone, mersalyl, neptal, and salyrgan were given in 2 c.c. doses intravenously (197 times), and intramuscularly (110 times). Mersalyl, neptal, and salyrgan were tried orally in tablet form, and novurit and salyrgan were tested as a rectal suppository. Eleven methods of enhancing the diuretic effects of mercurial salts were also tested, and 507 observations were devoted to this problem. The results of this investigation are as follows:

Neptal and esidrone when given intravenously or intramuscularly produced the largest diuresis, rather larger than salyrgan and much larger than mersalyl.

The intravenous method almost always induced greater diuresis (average diuretic index of 76) than the intramuscular method (average diuretic index of 56).

Of the two rectal suppositories tried, novurit gave much better results than salyrgan.

Neptal tablets by mouth proved more efficient (average diuretic index of 32) than mersalyl tablets (average diuretic index of 19), salyrgan tablets, or novurit suppositories rectally (each with a diuretic index of 17). Ammonium chloride was always given in association.

Although the urinary output after oral administration of a mercurial salt was greatest when 0 to 48 Gm. (three new tablets) of neptal were used, satisfactory diuresis was also produced by 0.32 g. (two new tablets).

Thirty grains (2 Gm.) of ammonium chloride given two hours before the administration of a mercurial preparation proved to be the best form of premedication. Enteric chocolate-coated tablets, each containing 7.5 grains (0.5 Gm.), proved the most convenient form of dispensing ammonium chloride.

In a patient confined to bed with heart failure and especially with edema, standard treatment would include the injection of a mercurial diuretic (2 c.c.) intravenously or intramuscularly every third day, preceded on each occasion by the administration of four tablets (30 grains or 2g) of ammonium chloride by mouth two hours before. During the ambulatory stage the patient should take neptal tablets (three in all, or 0.48 Gm.), twice weekly in the more severe case, and once a week in the less severe case, after the same premedication, and receive an intravenous or intramuscular injection (2 c.c.) at intervals according to need.

AUTHORS.

Miller, J. R., and Van Dellen, T. R.: Electrocardiographic Changes Following the Intravenous Administration of Magnesium Sulfate. III. Combined Effect With Digitalis. J. Lab. Clin. Med. **26**: 1116, 1941.

In the digitalized dog magnesium sulfate is capable of altering the contour of the T waves and producing a further delay in auriculoventricular conduction time in excess of that of digitalis or magnesium alone.

In the digitalized dog magnesium sulfate causes a brief increase in rate, followed by a slowing which approaches that obtained by digitalis. It is thus capable of overcoming the vagal stimulation produced by digitalis but for short periods only.

In the digitalized dog magnesium sulfate is capable of producing impulses of ectopic origin.

The results indicate that magnesium sulfate does not overcome the effects of digitalis intoxication but increases the degree of block and the occurrence of ectopic impulses.

AUTHORS.

Iglauer, A., and Altschule, M. D.: The Effect of Arterial and Venous Constriction Induced by Paredrine (p-Hydroxy-α-Methylphenylethylamine Hydrobromide) on the Lung Capacity and Its Subdivisions. Am. J. M. Sc. **201**: 664, 1941.

The subdivisions of the pulmonary volume were measured in seven experiments on five normal subjects after the administration of paredrine.

No significant deviation from the control values occurred.

Paredrine therefore does not produce marked changes in the blood content of the capillaries of the lungs.

AUTHORS.

Hueper, W. C., and Ichniowski, C. T.: Experimental Studies in Cardiovascular Pathology. II. Pathologic Lesions in Organs of Cats, Guinea Pigs, and Frogs, Produced by Digitalis Poisoning. J. Lab. and Clin. Med. **26**: 1565, 1941.

The introduction of single lethal doses of digitalis glycosides into guinea pigs, as well as of repeated sublethal doses of the drug into cats, results in the production of degenerative and necrotic myocardial and extracardiac (cerebral, suprarenal, hepatic, renal) organic lesions in the majority of the animals treated.

Some of the animals, however, dying from the toxic effects of the digitalis glycosides show at death no appreciable, or only minor cardiac, changes, while the extracardiac, and particularly cerebral, lesions are well developed.

The anatomic evidence obtained indicates that subacute and delayed death from digitalis poisoning may be the result of anatomic, myocardial lesions of severe type or, in the absence of these, of extracardiac cerebral or suprarenal lesions.

AUTHORS.

Modell, W., Gold, H., and Rothendler, H. H.: Use of Digitalis to Prevent Exaggerated Acceleration of the Heart During Physical Exercise in Patients With Auricular Fibrillation. J. A. M. A. **116**: 2241, 1941.

The average patient with auricular fibrillation has acceleration of ventricular rate during exercise chiefly, if not entirely, by decrease of the vagal tone. In these cases blocking the vagus by means of atropine accelerates the ventricles to the same maximum level as extreme physical exertion.

There is an indication that in some patients, especially those with advanced heart failure, an accessory mechanism for acceleration may also be invoked during extreme physical effort.

Exaggerated acceleration of the ventricles caused by physical exercise in patients with auricular fibrillation can be prevented in most cases by "extravagal" digitalization, a state in which the ventricles are slowed chiefly by the direct action of digitalis on auriculoventricular conduction and in which vagal tone has been, for the most part, lost. It is produced by relatively large doses of digitalis. In this state, the ventricular rate rarely exceeds 100 beats a minute after the vagi are blocked by atropine or after severe physical exercise.

The rate of the ventricles during rest does not disclose whether the digitalis has caused the slowing by the "vagal" or by the "extravagal" mechanism. There are two methods for determining "extravagal" digitalization: 1. the atropine test (the intravenous injection of 2 mg. of atropine sulfate) and 2. physical exercise. After neither of these tests will the ventricular rate rise appreciably above 100 beats a minute if enough digitalis has been given to cause slowing by the extravagal mechanism.

AUTHORS.

Book Reviews

THE HEART IN PREGNANCY AND THE CHILDBEARING AGE: By Burton E. Hamilton, M.D., Cardiologist to the Boston Lying-In Hospital, and K. Jefferson Thomson, M.D., Associate Physician, Metropolitan Life Insurance Co. Sanatorium, Mt. McGregor, New York, 1941, Little, Brown, and Co., Boston, 402 pages. $5.00.

This book is important both to cardiologists and obstetricians. It contains the observations of a careful physician who has been seeing and treating cardiac patients during pregnancy over a period of twenty years. Many interesting statistical studies of various aspects of this series of 850 cardiac patients are presented, although at times the deductions from the statistics do not appear conclusive because other interpretations seem to be equally reasonable. Much of the material has appeared in the authors' previous publications, but it is here collected and discussed at length.

The book is divided into three separate parts. The first part considers the diagnosis of heart disease in pregnancy; this is followed by Hamilton's conclusions as to prognosis and treatment, based upon his experiences at the Boston Lying-In Hospital.

Much space is given to a description of the diagnostic features of valvular disease, but too little space is devoted to a definition of the diagnosis of heart failure. It is not made clear at what stage of the process of cardiac insufficiency the authors would begin to apply the term "heart failure." Certain writers restrict this term to a condition associated with marked limitation of physical activity due to cardiac symptoms and associated with certain physical signs. That the authors do not have this condition in mind is apparent from the statement that "persistent râles are typically an early and sometimes subclinical sign of heart failure, appearing before the patient notices any change in her breathing." A history of heart failure, as related by the patient, must certainly depend upon a more marked degree of failure than this, so that the patient's history of heart failure and the demonstration of heart failure in the authors' clinic must obviously represent quite different degrees of the process. It does not seem, for this reason, that "the finding of a history or of signs of heart failure" should be used interchangeably as a basis for placing a woman in the class of "unfavorable" cardiacs.

Nevertheless, the method suggested for dividing cardiacs as to prognosis must have definite value because of the great difference in the mortality statistics between the "favorable" and "unfavorable" groups of patients with heart disease. Hamilton's statement that "any cardiac may fail at any time" suggests, however, that in his experience this method of dividing cardiacs does not serve to separate those who may develop failure from those who will not. It is the experience of most of those who have used the New York Heart Association classification that such a grouping is found in the patients with Class I Functional Capacity, and yet the authors see no value for prognosis in dividing cardiacs on the basis of functional capacity, as outlined by the New York Heart Association. Others, however, have found this method of value, and the final decision as to its usefulness must await further experience.

Hamilton obtains no assistance from observation of the patient after an effort test, and considers this "too harsh a method for estimating the state of delicate cardiacs in pregnancy." This seems to ignore the evident fact that there are

some cardiacs who are not delicate during pregnancy, and are able to carry on their accustomed household tasks, perhaps in addition to taking care of a numerous and troublesome family of children.

There are interesting observations on the influence of age and parity upon the prognosis of heart disease during pregnancy, and on the influence exerted by auricular fibrillation and other arrhythmias, and by serious complicating diseases, such as tuberculosis, syphilis, hypertension, pre-eclampsia and eclampsia, and pyelitis, upon the course of cardiac patients. The observation that heart failure seldom occurs for the first time at or following delivery has far-reaching implications which are developed in detail. Seventy-five per cent of the deaths, however, occurred during the puerperium, and 25 per cent occurred during pregnancy.

There is an important and practical discussion of the factors which may precipitate or contribute to heart failure, under the headings of infection, fatigue, gain in weight, anemia, and other less important and less frequent conditions. Also of great practical importance is the regime for the prevention of congestive heart failure. It is a detailed discussion of the directions to be given to the pregnant patient with cardiac disease in order to lessen the chance that she might develop heart failure. If we believe, as do the authors, that under a sufficiently severe strain "any patient with mitral stenosis may develop congestive failure suddenly, no matter how favorable the particular case may appear," then these restrictions must be applied to all cardiacs, as they recommend. Many cardiologists might feel that a weekly visit is more of a luxury than a necessity for many patients, but the authors do not believe so. They feel that it is particularly important from the end of the fifth to the end of the eighth month, a dictum in which all would join. By this close observation they have noted the development of congestive heart failure in 20 per cent of all their cardiacs at some time during pregnancy.

There is a very common-sense and realistic section on the part the physician should play in advising against pregnancy or in advising therapeutic abortion because of heart disease. Hamilton believes that it is not the physician's part to recommend, but that he should give his patient the benefit of his knowledge of the degree of risk involved in a case such as hers, and so help her to a decision as to the course she would desire to pursue.

There is an excellent chapter by Dr. F. C. Irving, on the principles and methods used for delivery of cardiacs at the Boston Lying-In Hospital. His observations on the features which favor abdominal section, as against induced labor, in the third to sixth month, on the desirability of avoiding hysterotomy in the later months, and of avoiding vaginal hysterotomy at all times, deserve serious consideration.

In the aftercare of cardiacs, emphasis is placed upon avoiding the administration of excessive fluid to those who show signs of heart failure. The harmlessness of nursing the infant is also emphasized. The authors' statistics on the rate of fetal mortality in this group of cases show a surprisingly high figure, even in the group of "favorable" cardiacs. To the knowledge of the reviewer, this has not before been prominently mentioned.

The second part of the book contains an important series of observations upon the variations of various circulatory functions during normal pregnancy, and the modifications of these functions that result from cardiac disease. Observations on the symptoms and clinical examination of a group of normal pregnant women are followed by observations on the heart size, as shown roentgenologically, the electrocardiogram, roentgenologic studies of the lungs and thorax, the vital capacity, the pulse and respiratory rate, the arterial pressure, venous pressure, circulation time, blood volume, and other features. Similar observations on a group of 99 pregnant cardiacs show the importance of vital capacity observation as an aid in the diagnosis of heart failure, and the possible usefulness of a measurement of total blood volume.

Book Three returns to the clinical aspects of heart disease in pregnancy, but particularly in women of the childbearing age who are not pregnant. The effects upon cardiacs of complicating diseases such as eclampsia, hypertension, and recurrent rheumatic fever are discussed, and also the effect of various valve lesions upon the prognosis. Congenital heart disease is discussed as it is observed in young women of the childbearing age, and the effects upon these patients of pregnancy and labor are pointed out.

This volume is an interesting exposition of Hamilton's conclusions from his experiences at the Boston Lying-In Hospital. It represents an important contribution to our knowledge of a small, and perhaps somewhat neglected, phase of cardiac disease.

HAROLD E. B. PARDEE.

ELEKTROKARDIOGRAPHIE FÜR DIE ÄRZTLICHE PRAXIS: By Prof. Dr. Erich Boden, Düsseldorf. Sechste Auflage, Band 14, Medizinische Praxis, 1941, Theodor Steinkopff, Dresden, 194 pages, 107 illustrations, R.M. 7.50.

This book is one of a set of twenty-nine volumes covering a wide range of both medical and surgical subjects, and was designed primarily for the general practitioner. It is a series of fifteen lectures—five on the theoretical and experimental aspects of electrocardiography, and ten on its practical application. The text is concise, and the illustrations are well chosen and beautifully executed. The volume quite adequately fulfills the purpose for which it was designed.

ROY W. SCOTT.

THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE: By fifty-six contributors, edited by William D. Stroud, M.D., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine, F. A. Davis Co., Philadelphia, 1940, 2 volumes, 1825 pages, 400 illustrations, $18.00.

These two volumes are the most monumental work that has yet appeared in the field of cardiovascular disease, and represent the cooperative endeavors of fifty-six well-known American authorities who are eminently qualified as clinicians, and, for the most part, as investigators of the subjects with which they deal. Few appraisals of the work will carry more weight than that given in the foreword by Sir Thomas Lewis, who writes: "The brilliant list of American authors of the present contents includes a score of names known in every part of the world where cardiovascular diseases have been intensively studied; they are known for the solid contribution of those who bear them to their subject. Rarely before have such a number of authoritative writers combined to place its views of a branch of medicine on record, and never before of cardiovascular disease; it is a guarantee to the reader that he is in direct or close contact with all the fountains of modern knowledge, the most important guarantee perhaps that any reader can be given."

Even if space permitted, the reviewer is not qualified to make a critical survey of each contribution in these volumes. Therefore, with a few exceptions, little more than an enumeration of the various subjects which are presented will be attempted, but even this will give the reader an idea of the scope of the work.

The introductory chapter, contributed by Sprague and White, deals in an able way with the classification of cardiovascular diagnosis. Since a correct diagnosis is the first step in sound therapy, a careful survey of the patient is imperative, and experience has taught that, in the field of cardiovascular disease, this is best accomplished by considering in each case (1) the etiologic factor or factors responsible for the disease, (2) the resulting anatomic changes in the heart and vessels, (3) the functional disturbances which are known to occur, and (4) the immediate or ultimate effect of the disease on the patient's ability to carry on. Under these four headings the authors list the various conditions which are observed clinically and at autopsy in cases of cardiovascular disease.

There follows a chapter on congenital cardiac abnormalities which needs no further commendation than to state that it was written by the late Maude E. Abbott, whose extensive and scholarly work in this field is known the world over. Rheumatic fever is discussed in three chapters; one is by McEwen, who presents, in a comprehensive way, rheumatic heart disease, with illustrative case reports; another, by Paul, is on the epidemiology; and a third is by Jones, who deals with a most important aspect of the subject, namely, evaluation of active infection. Whether a patient has an initial attack of rheumatic fever, a recrudescence of an earlier attack, or some other disease, is often a difficult diagnostic problem. Both clinical and laboratory evidences of active rheumatic infection are discussed by Jones.

A chapter on bacterial endocarditis, by Dock, is good as far as it goes, but too little attention is paid to the discussion of that most important type of endocarditis, namely, subacute bacterial endocarditis, which is usually caused by the implantation of the *Streptococcus viridans* on a scarred or congenitally deformed endocardium. An additional chapter covering this important subject would have enhanced the value of the treatise.

A sound, well-written chapter on cardiovascular syphilis is contributed by Paullin and Minnich, who rightly emphasize that syphilis is an important cause of heart disease only insofar as it involves the root of the aorta, and thereby leads to aortic insufficiency, dilatation of the aortic ring, or occlusion of coronary ostia. Stokes and Anderson cover the treatment of cardiovascular syphilis in a concise and adequate fashion. A chapter on the heart in hyperthyroidism is contributed by Thomas. At this point there might well have been a discussion of the myxedema heart, and why it was omitted is not clear. Conner writes on cardiac neurosis; Porter, on the heart in anemia; and Durant, on cor pulmonale. In a chapter entitled "The Cardiovascular System With Relation to the Kidneys," Hayman discusses the effect of hypertension on the heart and gives the best presentation of the problem of essential hypertension, in the light of recent experimental work, that is contained in the book.

A chapter on the heart in diseases of the glands of internal secretion was written by Barr, and cardiac trauma is handled by Barber. Porter has a chapter on acute pericarditis, and White one on chronic constrictive pericarditis. Roesler contributes a chapter on cardiac hypertrophy and dilatation, and Vander Veer one on chronic valvular heart disease. A clear presentation of coronary artery disease is given by Smith, and Levy writes on the diagnosis of coronary insufficiency, based largely on his experience with the anoxemia test. Stroud also writes a chapter on coronary disease; his remarks on treatment are notably sound and might well have been extended. A short chapter on nourishment of the heart by channels other than the coronary arteries was written by Bellet; the normal heart is discussed by King, and Levine writes on the cardiac patient as a surgical risk. Noteworthy for its lucidity and excellent illustrations is a chapter on heart sounds, by Wolferth and Margolies.

Done with characteristic thoroughness is a chapter on the form of the electrocardiogram, by Wilson, who is concerned with the cause and significance of the various deflections in the electrocardiogram, both normal and pathologic. There follows a well illustrated chapter by Bellet and McMillan on clinical electrocardiography, covering the clinical disorders of the heart beat, myocardial infarction, and other conditions resulting in abnormal electrocardiograms. The roentgenology of the heart and vessels is treated by Margolies, and the final chapter of Volume One, on disturbances of the heart beat, was written by Herrmann.

The first 318 pages of Volume 2 deal with various aspects of heart disease, and here we find several chapters on the general management of the cardiac patient. Stroud and Vander Veer write on the clinical efficacy of various digitalis preparations; Stroud writes on the cardiac patient in industry; Beck, on surgery of the heart and pericardium; Grant, on relief of pain in angina pectoris by paravertebral

sympathetic block with alcohol; Kerr, on the use of quinidine in cardiac irregularities; Blumgart and Riseman write on total thyroidectomy in the treatment of chronic heart disease, and Comstock and Stroud on physical therapy in cardiovascular disease. Marvin contributes an interesting chapter on the prevention and relief of heart disease as a public health problem, and points out that until we have more fundamental knowledge of human arteriosclerosis, we can speak with no assurance regarding the prevention of such common types of heart failure as hypertensive heart disease and coronary artery disease. Marvin also gives a review of the origin and aims of the American Heart Association, which is the one national organization concerned with all aspects of the problem of cardiovascular disease.

Bromer and Stroud write a chapter on congestive heart failure and one on left ventricular failure which review the modern concepts concerning pathogenesis and outline the management of the conditions. A chapter on the effects of digitalis on the electrocardiogram is contributed by McMillan, and Bellet and Weiss write on the heart and deficiency diseases.

The remaining 505 pages of Volume Two are devoted to peripheral vascular disease, starting with a comprehensive chapter by Allen on normal blood pressure and its variations. There follow a chapter on capillary circulation by DeGraff and Koffmann, and one on shock by Freeman.

Stieglitz writes a chapter on hypertensive arterial disease which conveys a somewhat obsolete view of the subject, in the light of the more recent experimental work of Goldblatt and his associates, which has demonstrated the role of the kidney in the etiology of arterial hypertension. Stieglitz' discussion of the subject is colored by his views on the pathogenesis of hypertension associated with arteriolar sclerosis, and is best summarized by quoting him verbatim: "What starts out as a purely physiological response becomes a progressive and destructive disease," and, elsewhere, "the anatomic physiologic changes of hypertensive arterial disease are the result rather than the cause of hypertension." Such categorical statements cannot be defended, since there is at present strong evidence in support of the view that arteriolar disease of the kidney, leading to renal ischemia, is the cause rather than the result of hypertension. Stieglitz tabulates a long list of predisposing and provoking factors which cause peripheral vascular spasm, and believes that, as the result of long continued hypertension, there follow, in order, first, hypertrophy, then degeneration, and, finally, fibrosis of the media, which he considers the essential lesions of arteriolar sclerosis. By most authorities, simple arteriosclerosis is regarded as primarily an intimal disease even when it affects the arterioles. In his discussion of the treatment of hypertension, Stieglitz makes no mention of hypertension associated with unilateral kidney disease. The logical and already successful treatment by excision of the diseased kidney in many cases is well known, and certainly merits consideration in any current discussion of hypertension.

In a chapter on psychic factors in arterial hypertension, Houston discusses the well-known effect of psychogenic factors on blood pressure levels, but, after reading the chapter, one feels that undue emphasis is placed on the role of the nervous system in causing hypertension and vascular disease. He, like Stieglitz, believes that the chief factor leading to arteriolar disease is hypertension, but unfortunately the problem of human arteriosclerosis is not so simple. For example, careful clinical and post-mortem studies show that negroes have more hypertension than whites, yet significantly less coronary artery disease. If hypertension were the major cause of vascular disease, obviously the negro should have more coronary disease than the white man. If worry and the strain of living were so important as Houston believes, it is indeed difficult to explain the fact that negroes, even in the deep South, have more hypertension than whites.

Barach writes a chapter on low arterial pressure which is eminently sound. He rightly emphasizes the fact that, in the absence of active disease, persons with low arterial pressures live longer than those with normal or high blood pressure.

Moschcowitz has a chapter entitled "Arteriosclerosis" which outlines the well-known pathologic changes, with remarks on pathogenesis, incidence, and localization of the affection, but in his discussion of the etiology of arteriosclerosis he is "groping in the dark for something in the dark." He would have us believe that hypertension is the sole cause of arteriosclerosis, according to the simple equation: arteriosclerosis = intravascular pressure × time. In his zeal to prove this thesis, he exhibits a wanton disregard for the old observation that (1) many elderly people with extensive and severe arteriosclerosis never had hypertension, and (2) that many middle-aged patients with coronary and cerebral artery sclerosis have a normal blood pressure. Would that the etiology of human arteriosclerosis were as simple as Moschcowitz claims! Considering the importance of the subject, his presentation of it leaves much to be desired.

A terse and adequate account of periarteritis nodosa is written by Farley, and a chapter on thromboangiitis obliterans is contributed by Buerger, whose extensive experience with this affection is plainly evident. A discussion of erythermalgia (erythromelalgia) of the extremities, lymphedema of the extremities, and sudden embolism and thrombosis of arteries of the extremities is adequately presented by Allen. Thrombophlebitis is handled by Barker, and acquired arteriovenous fistula, temporal arteritis, and aneurysm, by Hines. A sound and well-illustrated chapter on arteriosclerosis obliterans is written by Wright, who recognizes the nature of the problem, and, avoiding dogmatic assertions regarding the etiology, gives the reader a comprehensive account of the subject. Wright also contributes a chapter on Raynaud's syndrome and acrocyanosis, with colored illustrations that are outstanding. De Takats writes a chapter on vascular anomalies, and also one on varicose veins; both are well illustrated and adequately cover the subject. Volume Two closes with a scholarly discussion of the pathogenesis and treatment of edema, by Landis.

This treatise has the merits, as well as the disadvantages, which are inherent in a work by many authors. One finds considerable reduplication, which might be deleted; and a better arrangement of sequence of the chapters would considerably enhance the value of the book.

The various authors have made good use of illustrations and case reports, and the treatise has an excellent index. For the beginner, as well as for the physician who knows cardiovascular disease, but wants to know it better, this work has much to commend it.

ROY W. SCOTT.

NATURHEILKUNDLICHE BEHANDLUNG VON HERZKRANKHEITEN; ELEKTROKARDIOGRAPHISCHE STUDIEN: By Dr. Med et Phil. Franz Kienle, Assistant an der medizinischen Klinik der Rudolf Hess Krankenhaus, Dresden. Theodor Steinkopff, Dresden, 1940, 155 pages, 145 illustrations.

The author attempts to prove in this short monograph that nature healing is more effective in controlling myocardial failure and disturbances in heart rhythm than conventional therapy. The nature treatment consists of a liquid diet, followed by a soft diet, and later raw vegetables. Physical treatment consists of massage, warm arm- and foot-baths, carbonic acid baths in selected cases, and bandaging of the chest. In the introduction by Grote, credit is given to the late Reichsärzteführer, Dr. Gerhard Wagner, for the advocacy of the method. Electrocardiographic studies before and after treatment are presented in an attempt to prove the curative results. Only one case was reported in which there was failure of the method. Cases of myocardial failure of all types, extrasystoles, paroxysmal tachycardia, true and false bundle branch block, and heart block are reported. In his conclusion, Kienle states that nature healing will in great measure meet all requirements, and only rarely will it be necessary to introduce medical treatment.

The electrocardiographic interpretation is fanciful at times, especially when the author presents it as evidence of improvement.

The book can be recommended only as evidence that there is a new school of thought in Germany, wherein old and tested methods of therapy are scrapped in favor of *naturheilkundliche Behandlung*.

HAROLD FEIL.

HERZKRANKHEITEN, BAND 1: PHYSIOLOGIE, BEURTEILUNG, UND FUNKTIONELLE PATHOLOGIE DES HERZENS: By Prof. Dr. Max Hochrein, Direktor der Medizin, Universitäts Poliklinik, Leipzig. Theodor Steinkopff, Dresden and Leipzig, 1941, 480 pages, 170 illustrations.

This is a good exposition of diseases of the heart, chiefly from a physiologic point of view. The review includes many of the newer conceptions and is fairly comprehensive. Opening with a recapitulation of normal anatomy and physiology, Hochrein continues with clinical aspects, then follows with a full discussion of the pathologic physiology of diseases of the circulation. It is a sound work. The author presents to the German medical profession the currently accepted ideas about heart disease, including much English and American work.

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American Heart Association, Inc.

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THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

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